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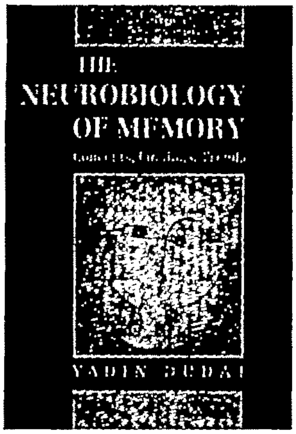

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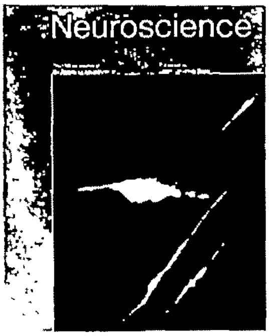

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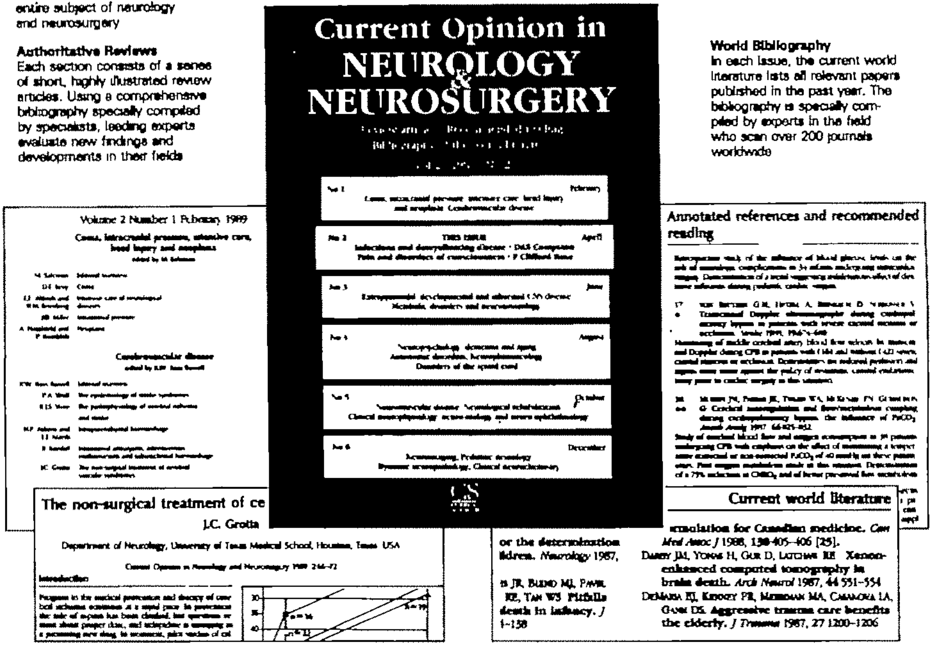
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SIMPLE REACTION TIMES TO LATERALIZED LIGHT FLASHES

VARIETIES OF INTERHEMISPHERIC COMMUNICATION ROUTES

by JEFFREY M. CLARKE *and* ERAN ZAIDEL

(*From the Department of Psychology, University of California, Los Angeles, USA*)

SUMMARY

Simple unimanual reaction times to lateralized light flashes were measured in 40 normal subjects, 4 commissurotomized patients, and a boy with callosal agenesis. In all subjects, reaction times tended to be shorter when the stimuli were presented on the same side as the response hand (uncrossed condition) than on the opposite side (crossed condition). In 2 experiments, the magnitude of the crossed-uncrossed difference (CUD) was greatest in the commissurotomized patients (ranging from 35 to 96 ms), the acallosal boy showed an intermediate CUD (20 and 12 ms for the first and second experiment, respectively), and normal subjects exhibited the smallest CUD (an insignificant 1 ms difference and a significant 3 ms difference in the first and second experiment, respectively).

For all subjects, reaction times increased when the stimulus light intensity was decreased (Experiment 1) or when stimulus eccentricity was increased (Experiment 2). However, the effects of these visual parameters on the CUD revealed group and individual differences. Neither stimulus light intensity nor eccentricity affected the CUD in the normals, in 1 of the commissurotomized patients, and in the acallosal boy. The CUDs in these subjects are attributed to the transfer of nonsensory information via the corpus callosum, via ipsilateral corticospinal tracts, and via the anterior commissure or ipsilateral motor pathways, respectively.

The CUDs of 2 commissurotomized patients varied with stimulus eccentricity but not intensity. Subcallosal interhemispheric visual transfer is thus apparently more sensitive to stimulus eccentricity than to intensity. The final commissurotomized patient, R.Y., had slower and less accurate responses to stimuli presented in the right visual hemifield during left, but not right, hand responses. An asymmetry in subcortical visual interhemispheric communication is suspected in this patient. The disparate results amongst these subjects are discussed and contrasted with previous findings. Finally, an information processing model of cortical and subcortical interhemispheric communication is presented.

INTRODUCTION

Poffenberger's (1912) simple reaction time procedure has been repeatedly used to measure neural conduction time between the cerebral hemispheres in normal subjects (*see* Bashore, 1981, for a review; Milner and Lines, 1982; Tassinari *et al.*,

Correspondence to: Mr J. M. Clarke, Department of Psychology, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, CA 90024-1563, USA.

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1983; St John *et al.*, 1987). Reaction times to lateralized light flashes are typically 2 to 6 ms longer when the light stimulus and the response hand are ipsilateral to each other (uncrossed condition) than when they are on opposite sides (crossed condition). According to Poffenberger, in the uncrossed condition the cerebral hemisphere that initially processes the visual stimulus also initiates the motor response. In the crossed condition, however, the receiving and the responding cerebral hemispheres are different, necessitating interhemispheric communication. Therefore the crossed-uncrossed difference (CUD) in reaction times appears to be a measure of interhemispheric transmission time across the corpus callosum in normal individuals. By testing patients that lack the cerebral commissures and by manipulating stimulus parameters, the nature of the neural information and the neural pathways responsible for the CUD in normals and disconnected patients can be examined.

Other callosal and noncallosal interhemispheric pathways, that may not be responsible for the CUD in normal subjects, are probably also conveying visual and nonvisual information in parallel. Patients with agenesis of the corpus callosum or following surgical transection of the cerebral commissures can indeed respond in the crossed condition. However, the CUD is abnormally large in these cases. Callosal agenesis patients typically exhibit 12 to 20 ms CUDs (Jeeves, 1969; Kinsbourne and Fisher, 1971; Reynolds and Jeeves, 1974; Milner, 1982; Milner *et al.*, 1985), while 2 patients with complete forebrain commissurotomies had 29 and 50 ms CUDs (Sergent and Myers, 1985). Furthermore, in 2 acallosal patients the CUD increased when the luminance of the stimulus was decreased—presumably evidence of noncallosal interhemispheric transfer of visual information (Milner, 1982; Milner *et al.*, 1985). Sergent and Myers (1985) demonstrated that the CUDs of 2 commissurotomized patients were unaffected by changes in stimulus light intensity. However, the manipulation of light intensity also failed to affect overall reaction times in these patients. It remains to be demonstrated whether a more effective stimulus manipulation can alter the CUD in commissurotomized patients. In normal individuals, changes in either stimulus light intensity or eccentricity affect overall reaction times but the CUD remains virtually unchanged—apparently evidence of callosal transfer of nonvisual (e.g., motor) information (Poffenberger, 1912; Berlucchi *et al.*, 1971, 1977; Milner and Lines, 1982; Lines *et al.*, 1984; St John *et al.*, 1987). Visual evoked potential findings further suggest that in normal subjects, the CUD represents interhemispheric transfer between motor, rather than visual, cortical areas (Lines *et al.*, 1984).

If the CUD of acallosal patients is indicative of interhemispheric transfer of visual information, then transfer is probably occurring across either the anterior commissure or a subcortical commissural pathway (Milner, 1982; Milner *et al.*, 1985). The anterior commissure is typically present and enlarged in acallosal patients (Loeser and Alvord, 1968; Bossy, 1970). Furthermore, interhemispheric transfer of visual information across the anterior commissure has been implicated in the monkey (Hamilton and Vermeire, 1986), in commissurotomized patients with intact anterior commissures (Risse *et al.*, 1978), and suspected in another case of callosal agenesis (Martin, 1985). Alternatively, subcortical commissural pathways may be responsible for the transfer. The posterior and intercollicular commissures connect the pretectal nuclei and the superior colliculi, respectively, both of which are involved in visual perception in the rat, cat, and macaque (Sprague, 1972; Sprague *et al.*, 1973). Trevarthen (1970) demonstrated that patients with complete cerebral commissurotomies, including sectioned anterior commissures, could cross-integrate visual information (e.g., line orientation and position) from the two visual hemifields. Rudimentary visual attributes of lateralized visual stimuli seem to be conveyed to the ipsilateral cerebral hemisphere via subcortical pathways.

To account for the effect of light intensity on the CUD in acallosal patients, Milner and Lines (1982) proposed that increasing stimulus light flux produces a concomitant increase in the rate of neuronal recruitment within visual pathways. Interhemispheric transfer between visual areas is therefore triggered more quickly for brighter stimuli. Presumably changes in stimulus light intensity have no effect on neural transmission time along nonvisual (e.g., motor) pathways. This view presupposes a decomposition of the information processing sequence into several functionally independent components, including separate stages of visual analysis and motor programming. In this manner, the visual and motor stages are modular (i.e., mutually impenetrable and encapsulated; Fodor, 1983). Thus a change in visual parameters of the task may affect visual analysis but no subsequent stages. If the CUD is invariant to the manipulation of a visual parameter, this does not necessarily imply nonvisual transfer. Transfer may be between visual areas that are far enough along not to be sensitive to the parameters used. Therefore, the CUD may be sensitive to other, untried or as yet undiscovered, visual parameters.

However, it is possible that the visual and motor stages are not modular. Transmission times for *nonvisual* pathways might therefore also be affected, cascade fashion, by changes in stimulus signal strength. In that case, the CUD in acallosal and commissurotomized patients could also result from either nonvisual interhemispheric transfer, or use of ipsilateral motor connections that are less effective than their contralateral counterpart (*see* Kinsbourne and Fisher, 1971; Zaidel, 1983; Jeeves and Milner, 1987; Trope *et al.*, 1987). Nevertheless, it may still be possible to determine whether transfer occurs along visual or nonvisual pathways by manipulating two, rather than one, visual stimulus parameters.

If stimulus intensity and eccentricity manipulations have equivalent effects on the CUD, then the findings may still be equivocal, depending on whether or not modularity holds. However, if intensity and eccentricity manipulations can be shown to have disparate effects on the CUD, while having comparable effects on overall reaction times, then transfer is probably occurring along visual pathways that are more sensitive to one of the two parameters (assuming the same pathway mediates transfer in both manipulations). Indeed, research on monkeys has shown that the anterior commissure interconnects temporal visual association areas

(Jouandet and Gazzaniga, 1979; Pandya and Rosene, 1985), that appear to be more concerned with object perception (i.e., 'what' a stimulus is) than spatial perception (i.e., 'where' a stimulus is; Ungerleider and Mishkin, 1982). If the anterior commissure is responsible for the CUD in acallosal patients, then the CUD may be more affected by changes in stimulus intensity than in stimulus eccentricity. On the other hand, while the superior colliculus has been shown to be sensitive to stimulus light flux, brightness, colour, and pattern, it plays a primary role in spatial analysis (Sprague *et al.*, 1973). In this case, variations in stimulus eccentricity may influence intercollicular transfer more than changes in light intensity.

In the present study the Poffenberger paradigm was used, and 40 normal subjects, 4 commissurotomized patients, and a boy with callosal agenesis were tested. Stimulus light intensity was varied in the first experiment, and stimulus eccentricity was manipulated in the second. The effects of these two different visual parameters on the CUD were examined in each group in turn.

SUBJECTS AND CASE REPORTS

Normal subjects

Forty undergraduate students, enrolled in an introductory psychology course at the University of California at Los Angeles, participated and earned course credit. In the first experiment there were 7 males (all right-handed) and 13 females (12 right-handed, 1 left-handed); in the second experiment, 6 males (4 right-handed, 2 left-handed) and 14 females (10 right-handed, 4 left-handed) were tested.

Commissurotomized patients

The 4 commissurotomized patients (L.B., N.G., A.A. and R.Y.) all received complete cerebral commissurotomies between 1963 and 1966 by Drs P. J. Vogel and J. E. Bogen for the treatment of intractable epilepsy. For all patients, the entire corpus callosum, anterior commissure, and hippocampal commissure were divided in a single operation. All the patients were right-handed. As indicated in Table 1, the subjects differed in sex, age, and IQ. Importantly, the subjects' age differed not only at the time of testing, but also at the onset of epileptic symptoms and at the time of surgery. Magnetic resonance (MR) images taken in 1987 showed complete section of the neocortical commissures and no evidence for primary visual or motor deficits likely to affect the outcome of the present experiment (Bogen *et al.*, 1988). Additionally, in none of the patients were there any indications of massive cerebral damage (e.g., to language areas) that would lead to reorganization of higher hemisphere functions. Further details concerning these patients' case histories can be found in Bogen and Vogel (1975).

Acallosal boy

Subject M.M. is a right-handed, 8-yr-old boy (in 1987) with developmental dyslexia. He was a patient of Dr Elena Boder, who provided the neurological information. CT and MR scans revealed extensive dilatation of the posterior and inferior horns of the lateral ventricles and absence of the corpus callosum. Physical and neurological examination was negative except for mild ataxia on tandem walking and slight nystagmus on lateral gaze. He was born 2 weeks later than expected, but otherwise his birth was normal. His developmental milestones were within the normal range, and he has had no serious illnesses. Based on psychological testing by Dr Karol Fishler, he has an

TABLE 1. SUMMARY OF CASE HISTORIES OF COMMISSUROTOMIZED PATIENTS

Patient	*Sex*	*Surgery*	*Age at onset of symptoms (yrs)*	*Age at surgery (yrs)*	*Age at testing (1987) (yrs)*	*IQ history*[a]	
						Preop.	*Postop.*
N.G.	F	Complete cerebral commissurotomy: single stage midline section of anterior commissure, corpus callosum (and presumably psalterium), massa intermedia and right fornix. Surgical approach by retraction of the right hemisphere	18	30	53	Wechsler-Bellevue 76(79,74)	WAIS 77(83,71) at age 35
L.B.	M	As above but massa intermedia absent	3:6[b]	13	35	WISC 113(119,108) at age 13	WAIS 106(110,100) at age 14
A.A.	M	Same as patient N.G. Difficult operation	5:6	14	36		WAIS 78(77,82) at age 17
R.Y.	M	Same as patient N.G.	17	43	63		WAIS 90(99,79) at age 45

[a] WISC and WAIS scores are expressed: full scale IQ (verbal IQ, performance IQ). [b] Age expressed as years : months.

average to above average intelligence for a boy his age (WISC-children-R: 96 (full scale), 95 (verbal), 98 (performance); Peabody picture vocabulary test IQ: 118; Raven Progressive Matrices: 80th percentile; all at 7 yrs, 5 months of age). Interestingly, his father also has developmental dyslexia but he is neuroanatomically normal as revealed by MRI.

EXPERIMENTS

Apparatus

The experiments were run on an IBM-XT compatible personal computer, with stimuli being displayed on an Amdek-310A CRT monitor. Assembly language programs, adapted from Smith and Puckett (1985), were implemented, enabling the measurement of reaction times to within an accuracy of 0.1 ms. A 'Treadlite' pad switch, positioned at the subject's midline, served as the response key.

Procedure

Subjects were tested individually in a dimly lit room. Head movements were minimized by the use of a chin rest, and care was taken to keep the patients' hands and feet apart to discourage cross-cueing strategies. Each subject was instructed to press the response key as quickly as possible with the index finger of the response hand whenever a light flash appeared on the CRT screen. Responses were monitored to ensure that a finger, rather than a wrist or arm, movement was being used to depress the response key. All subjects were tested binocularly. The importance of fixation on a centrally located cross was stressed and monitored both at the onset of the experiment and throughout the experiment.

Experiment 1: light intensity manipulation

In the first experiment, light flashes (ASCII character 220) subtending a visual angle of 0.33° appeared 4° to the left or right of a centrally located fixation cross (0.33° in width). The light flashes appeared in one of two intensities: 54.82 cd/m^2 or 0.63 cd/m^2, against a 0.02 cd/m^2 background (measured using a Spectra Prichard photometer—model PR 1970, with a PD 1962 lens, using a 30′ spot size). The fixation cross itself had an intensity of 0.63 cd/m^2 and remained on the screen throughout the experiment. A given trial began with the presentation of a 1000 Hz tone for 250 ms, which served as a cue to fixate. Next, a delay, varying randomly from 500 ms to 1500 ms preceded a 35 ms light flash (20 ms actual display + approximately 15 ms phosphor decay). A 3 s interval separated trials. Response times were measured from the onset of stimulus presentation. Intensity and the hemifield of presentation varied pseudorandomly, such that there were 20 presentations of each of the four Visual Hemifield × Intensity conditions for every block of trials. Each subject responded to 40 practice trials (20 trials for each hand), and then received 10 blocks of 80 trials. Additional trials were automatically added to the end of a block whenever a reaction time was less than 150 ms (considered an anticipatory error) or greater than 1000 ms (considered an error of inattention). To counter effects of fatigue, a maximum of 20 make-up trials were permitted for each block of trials, and subjects were encouraged to rest briefly between blocks of trials. The response hand was alternated after every block, and the subjects were counterbalanced as to the initial responding hand.

Experiment 2: stimulus eccentricity manipulation

The second experiment was identical to the first except that instead of varying light intensity, stimulus eccentricity from fixation was manipulated. The light flashes appeared either 4° or 10° to the left or right of a centrally located fixation cross. Both the light flashes and the fixation cross were presented at a midrange light intensity of 3.94 cd/m^2, against a 0.02 cd/m^2 background. The visual hemifield and eccentricity in which a light flash appeared varied pseudorandomly within a block of trials. As in the first experiment, a total of 40 practice trials and 10 blocks of 80 error-free test trials were obtained from each subject.

For each subject, an experimental session lasted about an hour. For all patients, a period of several months separated the two experiments.

Analyses

In each experiment there were 8 conditions (Hand × Visual Hemifield × Intensity or Eccentricity). Any reaction time that was greater than 3 SD from its respective condition mean for that subject (collapsed across blocks of trials) was removed from the analysis. These outliers probably represent momentary shifts in attention, and as such would only confound attempts to measure neural conduction time.

For the normal subjects, the same statistical results were obtained whether subject means or medians were used. The results from the analysis of subject means will be reported. Each of the 20 normal subjects, from the respective experiments, contributed 8 condition means, collapsed across blocks of trials, towards a 3-way analysis of variance. Between-subject variables included gender for the intensity experiment, and gender and handedness for the eccentricity experiment.

The data from each patient were analysed separately. Individual reaction times were coded as belonging to 1 of the 8 conditions and then submitted to a 3-way analysis of variance that treated trials as the random variable.

RESULTS

Mean reaction times and standard errors for each of the 8 conditions, for all subjects, are presented in Tables 2 and 3 for Experiments 1 and 2, respectively. A summary of the principal statistical outcomes from both experiments and all subjects are presented in Table 4.

TABLE 2. MEAN REACTION TIMES (ms) AS A FUNCTION OF STIMULUS LIGHT INTENSITY, RESPONSE HAND AND THE VISUAL HEMIFIELD IN WHICH THE STIMULI APPEARED FOR 20 NORMAL SUBJECTS, 4 COMMISSUROTOMIZED PATIENTS, AND AN ACALLOSAL BOY (M.M.)

		Low light intensity				*High light intensity*			
		Left hand		*Right hand*		*Left hand*		*Right hand*	
Subject(s)		*LVF*	*RVF*	*LVF*	*RVF*	*LVF*	*RVF*	*LVF*	*RVF*
Normals	Mean	324.6	326.9	325.5	327.9	295.1	295.4	297.8	293.9
	SE	7.2	7.7	7.5	8.3	7.3	6.9	7.8	7.4
L.B.	Mean	355.7	371.5	372.4	314.8	314.7	330.8	332.2	280.6
	SE	3.5	3.6	3.3	4.3	3.2	2.7	3.3	3.3
N.G.	Mean	354.1	374.4	413.6	332.9	329.1	324.2	363.2	290.5
	SE	4.9	8.7	9.0	5.7	3.7	5.1	5.3	4.7
A.A.	Mean	612.8	647.8	678.9	583.0	547.0	571.6	601.6	515.6
	SE	17.2	20.9	18.3	15.7	15.6	16.0	14.3	13.5
R.Y.	Mean	429.5	504.8	429.5	402.5	391.9	542.4	401.8	374.0
	SE	6.2	12.0	5.7	7.7	5.2	15.5	5.9	5.8
M.M.	Mean	347.7	376.4	366.8	351.5	318.0	339.3	345.0	330.4
	SE	6.4	8.7	8.5	7.1	6.7	6.4	6.8	6.6

Means and standard errors (SE) were calculated across subjects for the normal subjects, and across trials for the patients. LVF = left visual hemifield; RVF = right visual hemifield.

TABLE 3. MEAN REACTION TIMES (ms) AS A FUNCTION OF STIMULUS ECCENTRICITY RESPONSE HAND AND THE VISUAL HEMIFIELD IN WHICH THE STIMULI APPEARED FOR 20 NORMAL SUBJECTS, 4 COMMISSUROTOMIZED PATIENTS, AND AN ACALLOSAL BOY (M.M.)

		4° eccentricity				*10° eccentricity*			
		Left hand		*Right hand*		*Left hand*		*Right hand*	
Subject(s)		*LVF*	*RVF*	*LVF*	*RVF*	*LVF*	*RVF*	*LVF*	*RVF*
Normals	Mean	297.5	303.8	298.5	300.7	314.3	319.5	315.7	314.0
	SE	6.2	6.7	6.9	6.8	7.6	8.3	8.2	8.1
L.B.	Mean	350.7	371.3	369.6	305.9	367.7	407.1	388.2	336.0
	SE	3.2	3.2	3.9	3.4	4.1	4.2	4.8	5.0
N.G.	Mean	379.3	373.3	447.3	351.5	393.8	406.5	465.6	344.6
	SE	4.2	5.8	7.6	5.9	5.5	7.5	7.0	4.8
A.A.	Mean	507.6	547.8	608.7	569.7	519.8	614.8	687.1	590.2
	SE	13.1	12.8	12.3	11.4	12.8	13.5	13.2	12.3
R.Y.	Mean	369.6	466.2	426.9	387.2	388.1	473.3	459.1	378.9
	SE	3.2	6.9	5.8	4.6	3.5	5.8	5.8	3.5
M.M.	Mean	353.6	369.6	363.9	360.1	362.2	380.0	394.3	382.0
	SE	5.0	5.4	4.8	5.0	5.0	5.2	7.0	5.0

Means and standard errors (SE) were calculated across subjects for the normal subjects, and across trials for the patients. LVF = left visual hemifield; RVF = right visual hemifield.

TABLE 4. SUMMARY OF SIMPLE REACTION TIME RESULTS FOR THE NORMAL SUBJECTS, THE 4 COMMISSUROTOMIZED PATIENTS, AND THE ACALLOSAL BOY (M.M.), FOR EXPERIMENT 1 IN WHICH STIMULUS INTENSITY (I) IS MANIPULATED AND FOR EXPERIMENT 2 IN WHICH STIMULUS ECCENTRICITY (E) IS MANIPULATED

	*RT in normal range?**		*Main hand effect?*		*Main VF effect?*		*Main effect of visual parameter?*		*Effect of I or E on CUD?*		*Size of CUD (ms)*	
Subject(s)	*I*	*E*	*I*	*E*	*I*	*E*	*I*	*E*	*I*	*E*	*I*	*E*
Normals	+	+	−	−	−	−	+	+	−	−	1.0	2.8
L.B.	+	+	R	R	R	R	+	+	−	−	35.1	43.7
N.G.	+	+	−	L	R	R	+	+	−	+	42.2	55.8
A.A.	−	−	−	L	R	−	+	+	−	+	59.5	68.0
R.Y.	−	−	R	R	L	L	+	+	+	+	71.5	75.4
M.M.	+	+	−	L	−	−	+	+	−	−	19.8	12.4

* Overall uncrossed reaction times that are < 2 SD from the grand mean of the normals are considered within the normal range. RT = reaction time; VF = visual hemifield; CUD = crossed-uncrossed difference in reaction time. + = yes; − = no. An R or L is equivalent to a + and indicates which hand/VF condition had the faster reaction time.

Normal subjects

An average of 1.8% and 2.5% of the trials from experiments 1 and 2, respectively, were excluded as either errors of inattention or anticipation. Males responded an average of 31.7 ms faster than females in the eccentricity experiment (F(1,18) = 5.08, $P < 0.05$), while there was no significant main effect of gender in the intensity experiment. There was no significant effect of handedness, nor any significant interactions involving handedness or gender. The data were therefore collapsed across handedness and gender variables and reanalysed without these variables.

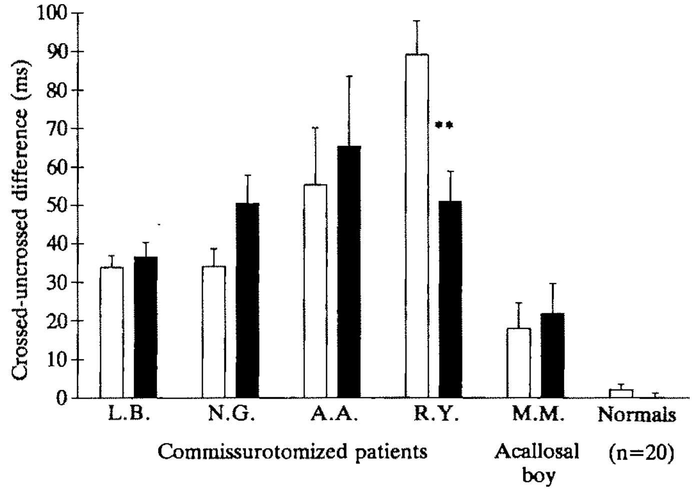

FIG. 1. Experiment 1. Mean crossed-uncrossed difference in reaction times and SE bars for 20 normal subjects, 4 commissurotomized patients, and a boy with callosal agenesis at 2 stimulus light intensities. Bright intensity: open bars; dim intensity: solid bars. $^{**}P < 0.01$.

The main effects of Hand and Visual Hemifield were not significant for either experiment. Reaction times were an average of 30.6 ms faster for bright than for dim light flashes in Experiment 1 (F(1,19) = 600.85, $P < 0.0001$). For Experiment 2, responses to stimuli at 4° eccentricity were an average of 15.7 ms faster than to those at 10° eccentricity (F(1,19) = 61.64, $P < 0.0001$). The overall CUD for the intensity experiment was 1.0 ms. However, the Hand × Visual Hemifield interaction, which gives rise to the CUD, was not significant F(1,19) = 1.39, $P > 0.05$). For the eccentricity experiment the Hand × Visual Hemifield interaction was significant F(1,19) = 10.84, $P > 0.01$), with a mean CUD of 2.8 ms. No other interactions proved significant for either experiment. Since the 3-way interactions (Hand × Visual Hemifield × Intensity or Eccentricity) were not significant, visual stimulus parameter manipulations, that affected overall reaction times, had no effect on the CUD, as can be seen in figs 1 and 2.

As the data from each patient were analysed separately, similar analyses were carried out on the data from each normal subject for comparative purposes. For the intensity experiment, the CUD was a positive value for 13 subjects and a negative value for 7 ($P = 0.13$, 1-tailed sign test); the Hand × Visual Hemifield interaction was not significant for any subject. In the eccentricity experiment, the CUD was positive for 16 subjects and was negative for 4 ($P < 0.01$, 1-tailed sign test). Only 2 subjects demonstrated significant ($P < 0.05$) Hand × Visual Hemifield interactions in the eccentricity experiment, and these subjects had CUDs of 7.0 ms and 7.3 ms. Overall, negative CUDs were evident in 3 of the 7 left-handed subjects, but only in 8 of the 33 right-handed subjects.

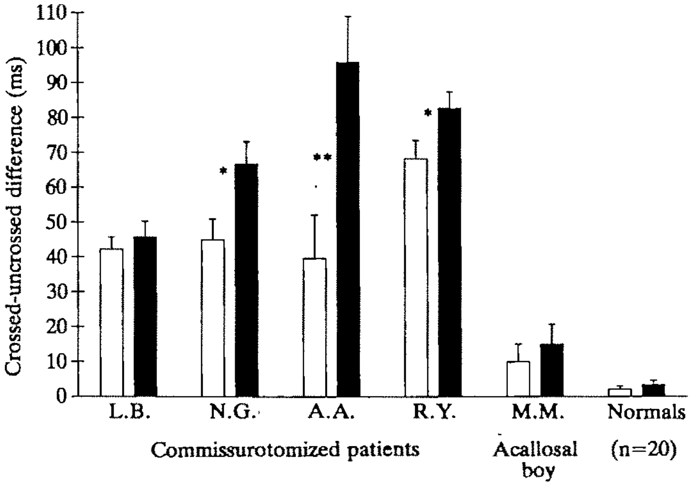

FIG. 2. Experiment 2. Mean crossed-uncrossed difference in reaction times and SE bars for 20 normal subjects, 4 commissurotomized patients, and a boy with callosal agenesis at 2 stimulus eccentricities. 4° eccentricity: open bars; 10° eccentricity: solid bars. $*P < 0.05$; $**P < 0.01$.

The results from the Sergent and Myers (1985) study indicate that overall reaction times are longer and more variable for the 2 commissurotomized subjects (N.G. and L.B.) than for the single normal subject they tested. The larger number of normal and commissurotomized subjects tested in this study affords a verification of this observation. For each normal subject an overall reaction time was derived, and these times were averaged across subjects yielding grand mean reaction time values of 310.9 ms (SD = 32.6) for the intensity experiment and 308.0 ms (SD = 31.8) for the eccentricity experiment. In a similar manner, for each normal subject the SD of the overall reaction time was determined, and these values were averaged resulting in a grand mean 'standard deviation' of 52.9 ms (SD = 16.6) and 50.1 ms (SD = 14.5) for the intensity and the eccentricity experiments, respectively.

Commissurotomized patients

The most pervasive and consistent finding among the commissurotomized subjects was the large CUDs, ranging from 35 ms to 96 ms over both experiments. While reaction times and variances were within the normal range for some of the patients, the CUDs were at least 8 SDs from normal values for every commissurotomized patient.

Patient L.B.

This patient had a low percentage of trials omitted as anticipatory or attentional errors (0.9% Experiment 1, 1.8% Experiment 2). Overall reaction times and variability in these reaction times are comparable to those of the normal subjects. The overall reaction times are 0.7 and 1.7 SDs from the grand means of the normal subjects for Experiments 1 and 2, respectively. Similarly, the overall variances in responding are less than 1 SD from the normals' means.

For both the intensity and the eccentricity experiments, responses were made faster with the right hand (F(1,778) = 56.56, $P < 0.0001$ and F(1,778) = 72.33, $P < 0.0001$, respectively), and were shorter during right visual hemifield presentations (F(1,778) = 64.00, $P < 0.0001$ and F(1,778) = 23.92, $P < 0.0001$, respectively). In Experiment 1, reaction times were 38.9 ms faster for bright than for dim light flashes (F(1,778) = 261.06, $P < 0.0001$), while in Experiment 2, responses were 24.8 ms faster for light flashes at 4° than at 10° eccentricity (F(1,778) = 78.95, $P < 0.0001$). The Visual Hemifield × Eccentricity interaction was significant (F(1,778) = 7.07, $P < 0.01$), indicating that responses were made more quickly for right visual hemifield than for left visual hemifield presentations at 4° eccentricity, while there was no significant difference between the hemifields at 10° eccentricity. Significant Hand × Visual Hemifield interactions were demonstrated in Experiments 1 and 2 (F(1,778) = 212.58, $P < 0.0001$ and F(1,778) = 237.26, $P < 0.0001$, respectively). Crossed responses were an average of 35.1 ms and 43.7 ms slower than uncrossed responses for the intensity and the eccentricity experiments, respectively. The 3-way interaction was not significant for either of the experiments, suggesting that changes in visual parameters that influence overall reaction times have no effect on the CUDs in this patient, as can be seen in figs 1 and 2.

In summary, L.B.'s reaction times are within the normal range. He displayed a right hand and right visual hemifield advantage, and his abnormally large CUDs (35 and 44 ms) are unaffected by changes in stimulus intensity or eccentricity, despite significant effects of these parameters on overall reaction times.

Patient N.G.

Anticipatory and attentional errors accounted for 3.5% and 2.8% of all trials for Experiments 1 and 2, respectively. Like L.B., overall reaction times and variability in responding are within normal limits. Reaction times are 1.1 and 2.7 SDs from the means of the normals for the intensity and the eccentricity experiments, respectively (or 0.5 and 1.9 SDs, respectively, if only uncrossed reaction times are considered). The overall variances are less than 2 SDs from that of the normals for both experiments (or less than 1 SD when only uncrossed reaction times are evaluated).

N.G. responded significantly faster with the left than with the right hand during the eccentricity experiment (F(1,775) = 10.45, $P < 0.01$), while there was no significant difference between the hands in the intensity experiment. Reaction times were faster for right, compared with left, visual hemifield presentations for both the intensity experiment (F(1,777) = 63.03, $P < 0.0001$) and the eccentricity experiment (F(1,775) = 146.21, $P < 0.0001$). The intensity and eccentricity manipulations were significant (F(1,777) = 93.32, $P < 0.0001$ and F(1,775) = 11.52, $P < 0.001$, respectively). Responses averaged 42.1 ms faster for bright than for dim stimuli, and were 14.5 ms faster for 4° than for 10° eccentricity. A significant Hand × Eccentricity interaction (F(1,775) = 4.35, $P < 0.05$) indicated that the left hand was faster than the right for stimuli at 4° eccentricity, while there was no significant difference between the hands for 10° eccentricity. The Hand × Visual Hemifield interaction was significant for both the intensity and the eccentricity experiments (F(1,777) = 94.49, $P < 0.0001$ and F(1,775) = 165.47, $P < 0.0001$, respectively), resulting in CUDs of 42.2 ms and 55.8 ms, respectively. The Hand × Visual Hemifield × Intensity interaction did not reach significance in Experiment 1 (F(1,777) = 3.63, $P = 0.057$), while there was a significant 3-way (Hand × Visual Hemifield × Eccentricity) interaction in Experiment 2 (F(1,775) = 6.38, $P < 0.025$). In Experiment 2, the CUD was 21.9 ms smaller for stimuli at 4° than at 10°, as presented in fig. 2.

In summary, N.G.'s reaction times are within normal limits, at least for those trials that did not require interhemispheric transfer. She had a right visual hemifield advantage and no consistent hand advantage. The CUD did not significantly differ for the two stimulus light intensities (M = 42 ms), but was significantly larger for stimuli at 10° eccentricity (67 ms) than at 4° eccentricity (45 ms).

Patient A.A.

This patient had greater difficulty maintaining attention compared with the other patients, and 29.0% and 15.6% trials were omitted as errors from Experiments 1 and 2, respectively. To determine whether there were any systematic patterns in error responses, statistical tests were conducted. The proportion of trials with errors, excluding make-up trials, was determined over each Hand × Visual Hemifield × Intensity or Eccentricity condition for every block of trials. These values were analysed using a 3-way repeated measures analysis of variance, where consecutive pairs of left and right hand blocks served as the random variable (i.e., 5 pairs of blocks). Significant ($P < 0.05$) results for the intensity experiment included more errors for left than right hand responses, dim compared with bright stimuli, and crossed versus uncrossed conditions. There were no significant findings for the eccentricity experiment.

Reaction times and variances fell well outside normal values, ranging from

6-9 SDs from those of the controls for both experiments. Similar findings are evident when only uncrossed responses are examined.

Left hand responding was faster than right in the eccentricity experiment ($F(1,755) = 54.42$, $P < 0.0001$) while there was no significant main effect of hand in the intensity experiment. However, the patient took rest breaks after every block of trials in Experiment 1, while in Experiment 2, rest periods occurred only after completion of a left followed by a right hand block of trials. Right hand responses were slower in Experiment 2 probably because the patient began to tire during these blocks of trials. Responses were faster for right compared to left visual hemifield presentations in the intensity experiment ($F(1,687) = 6.92$, $P < 0.01$), while the difference was not significant for the eccentricity experiment. In Experiment 1, responses to stimuli of the lower intensity were an average of 71.5 ms slower than to bright stimuli ($F(1,687) = 38.02$, $P < 0.0001$). Similarly in Experiment 2, reaction times were an average of 45.4 ms slower to light flashes at 10° eccentricity than to those at 4° eccentricity ($F(1,755) = 24.50$, $P < 0.0001$). The Hand × Visual Hemifield interaction was significant for both Experiments 1 and 2 ($F(1,687) = 26.99$, $P < 0.0001$ and $F(1,755) = 56.64$, $P < 0.0001$, respectively), revealing CUDs of 59.5 ms and 68.0 ms, respectively. While the Hand × Visual Hemifield × Intensity interaction was not significant, the Hand × Visual Hemifield × Eccentricity interaction was significant ($F(1,755) = 9.80$, $P < 0.01$). The CUD was 56.4 ms smaller for stimuli at 4° than at 10° eccentricity, as can be seen in fig. 2.

In summary, A.A.'s reaction times are unusually long and variable. There was no consistent hand or visual hemifield advantage across the 2 experiments. Like patient N.G., the CUD was not significantly affected by stimulus intensity ($M = 60$ ms), but was larger for stimuli at 10° (96 ms) than at 4° (40 ms) eccentricity.

Patient R.Y.

This patient would periodically not respond to a light flash despite his appearance of being alert. There were 19.4% trials with errors in the intensity experiment and 4.1% in the eccentricity experiment. Errors were statistically analysed in the same manner as for patient A.A. In the intensity experiment there were more errors for left than right hand responses, right than left visual hemifield presentations, and dim compared with bright stimuli. Significant interactions included Hand × Visual Hemifield (more errors for the right visual hemifield-left hand (RVF-Lh) condition than all other conditions); Hand × Intensity (more errors for Lh-dim intensity condition than the other 3 conditions); and Visual Hemifield × Intensity (more errors were made to dim than to bright light flashes in the right visual hemifield, while the difference was not significant in the left visual hemifield). For the eccentricity experiment, more errors were made to right than left visual hemifield presentations, and only the 3-way interaction was significant. Significantly more errors were made in the RVF-Lh-4° eccentricity condition than the 7 other conditions, which did not significantly differ from one another.

Overall reaction times are 3.7 and 3.5 SDs from that of the normal grand mean for Experiments 1 and 2, respectively (or 2.7 and 2.3 SDs for uncrossed reaction times). For Experiments 1 and 2, variances in reaction times are 2.6 and 1.0 SDs from mean normal values (or less than 1 SD for both experiments when only uncrossed reaction times are considered).

For the intensity and the eccentricity experiments, right hand responding was faster than left ($F(1,726) = 123.08$, $P < 0.0001$ and $F(1,776) = 10.02$, $P < 0.01$, respectively), and reaction times were faster to stimuli in the left visual hemifield compared to those in the right ($F(1,726 = 52.82$, $P < 0.0001$ and $F(1,776) = 18.91$, $P < 0.0001$, respectively). Stimuli of brighter intensity were responded to 11.4 ms more quickly than less intense stimuli ($F(1,726) = 5.74$, $P < 0.025$). Reaction times to stimuli at 4° eccentricity were an average of 12.6 ms faster than those at 10° eccentricity ($F(1,776) = 12.04$, $P < 0.001$). The Hand × Visual Hemifield interaction was significant for both Experiments 1 and 2 ($F(1,726) = 142.35$, $P < 0.0001$ and $F(1,776) = 448.55$, $P < 0.0001$, respectively), resulting in respective CUDs of 71.5 ms and 75.4 ms.

For the intensity experiment, all other interactions were significant: Hand × Intensity ($F(1,726) = 5.74$, $P < 0.025$), Visual Hemifield × Intensity ($F(1,726) = 10.00$, $P < 0.01$), and Hand × Visual Hemifield × Intensity ($F(1,726) = 10.45$, $P < 0.01$). These latter results reflect the surprising finding that reaction times were *longer* for bright than for dim light flashes for the RVF-Lh condition, as can be seen in Table 2. All other Hand × Visual Hemifield conditions had shorter reaction times to bright than to dim light flashes as would be expected. This resulted in a larger CUD for bright light flashes (M = 89.1 ms) than for dim light flashes (M = 51.1 ms), as shown in fig. 1.

Results from the eccentricity experiment indicate a significant Visual Hemifield × Eccentricity interaction ($F(1,776) = 13.29$, $P < 0.001$) and a significant Hand × Visual Hemifield × Eccentricity interaction ($F(1,776) = 4.15$, $P < 0.05$). Simple effects on the 3-way interaction indicate that the LVF-Rh condition was significantly affected by stimulus eccentricity, while the other crossed condition (RVF-Lh) was not significantly affected. Therefore, while the CUD was greater for stimuli at 10° eccentricity (M = 82.7 ms) than for stimuli at 4° eccentricity (M = 68.2 ms), the RVF-Lh condition did not have a significant contribution to this effect.

In summary, R.Y. had an idiosyncratic pattern of results. His reaction times are unusually long compared to the student controls, but are probably within the normal limits for someone his age. He had problems responding to stimuli in the right visual hemifield when he used his left, but not right hand, at least for stimuli presented at 4° eccentricity. This resulted in a right hand advantage and a left visual hemifield advantage across the two experiments. The CUD was paradoxically larger for bright (89 ms) than for dim (51 ms) light flashes. A larger CUD was found for stimuli at 10° (83 ms) than at 4° (68 ms) eccentricity, consistent with the results from N.G. and A.A.

Acallosal boy, M.M.

Most of M.M.'s errors were of the anticipatory type, accounting for 7.4% and 1.6% of the trials in Experiments 1 and 2, respectively. Errors of inattention accounted for 3.6% of the trials in the intensity experiment and 1.1% of all trials in the eccentricity experiment. Errors were equally distributed across all conditions. Overall reaction times and variances are less than 2 SDs from the normal means for both experiments.

Left hand responses were significantly faster than right during the eccentricity experiment (F(1,776) = 5.36, $P < 0.025$), while there was no significant difference in the intensity experiment. No significant main effect of Visual Hemifield was evident for either experiment. Reaction times were 27.4 ms faster for bright than for dim light flashes (F(1,772) = 29.08, $P < 0.0001$), and were 17.8 ms faster for stimuli at 4° compared to 10° eccentricity (F(1,776) = 22.27, $P < 0.0001$). For both Experiments 1 and 2, significant Hand × Visual Hemifield interactions were demonstrated (F(1,772) = 15.36, $P < 0.001$ and F(1,777) = 10.89, $P < 0.01$, respectively). The respective CUDs of 19.8 ms and 12.4 ms, for the intensity and the eccentricity experiments, are notably larger than those of the normal subjects (4.9 and 2.6 SDs from the normal means, respectively) and yet are considerably smaller than those of the commissurotomized patients. The only other significant interaction was that of Hand × Eccentricity (F(1,776) = 4.88, $P < 0.05$). Reaction times were significantly faster for stimuli at 4° compared with 10° eccentricity when the left hand was used, while this difference was not significant for right hand responses. Changes in stimulus intensity or eccentricity did not significantly alter the CUD as indicated by the nonsignificant 3-way interaction from each experiment.

In summary, M.M.'s reaction times were within the normal range. There was no visual hemifield effect and no consistent hand effect for the 2 experiments. His CUDs (20 and 12 ms) fell between the values from the normals and the commissurotomized patients. Neither stimulus intensity nor stimulus eccentricity significantly affected the CUD, although overall reaction times were affected.

DISCUSSION

The CUDs from both the intensity and the eccentricity experiments were found to increase from normals (1 ms nonsignificant difference and 3 ms difference for the 2 experiments, respectively), to the acallosal subject (20 and 12 ms, respectively), with the CUD being the greatest in the commissurotomized patients (ranging from 35 to 96 ms across the 2 experiments). The manipulations of stimulus intensity and eccentricity provide a means of assessing whether visual or nonvisual interhemispheric pathways are involved. In the normal subjects, neither stimulus intensity nor eccentricity affected the CUD, as has been demonstrated previously (Berlucchi *et al.*, 1971, 1977; Milner and Lines, 1982). However, St John *et al.* (1987) did find an eccentricity effect in normal subjects. As these authors point out, the differences were small (e.g., 0.9 ms greater CUD for 2° versus 15° eccentricity), and the effect was not apparent in the majority of the subjects. Thus in normal individuals, the CUD may represent the interhemispheric transfer time of nonsensory information across the corpus callosum.

The nonsignificant CUD for the normals in Experiment 1 and the finding that several normal subjects had negative CUDs is probably a product of the relatively large variances in reaction times given the magnitude of interhemispheric transfer time. Furthermore, the CUD has been shown to vary with gender (St John *et al.*, 1987) and handedness (McKeever and Hoff, 1979, 1983; Levy and Wagner, 1984). A similar handedness effect was also apparent in the present study. Negative CUDs were observed in 43% of the left-handed subjects, but only in 24% of the right-handers. Given that males and females, and left and right-handers were tested in the present study, a more homogeneous sample, and more trials per subject, would probably have yielded smaller overall variances in response times, and subsequently more consistent measures of the CUD.

The CUDs observed in commissurotomized patients L.B. (35 and 44 ms) and N.G. (42 and 56 ms) are similar to values obtained by Sergent and Myers (1985) when they tested the same subjects (29 and 50 ms for L.B. and N.G., respectively). Sergent and Myers noted that the overall reaction times of these 2 patients were considerably larger, and variances greater than that of the single normal subject tested by them. However, in the present study 40 college students were tested, and both reaction times and variances of L.B. and N.G. were within normal limits, particularly when only uncrossed reaction times are considered. Sergent and Myers's manipulation of stimulus light intensity had no effect on either the CUD or overall reaction times for both L.B. and N.G. The light intensities used were apparently not sufficiently different to affect reaction times consistently. In the present study, manipulations of both stimulus light intensity and stimulus eccentricity significantly affected reaction times for all subjects. The surprising finding was that the patients differed in the effect that the visual parameters had on the CUD.

For both commissurotomized patients N.G. and A.A., the CUD was larger (by 22 ms and 56 ms, respectively) for 10° than 4° light flashes, while the CUD was not significantly affected by changes in stimulus intensity. However, the stimulus intensity manipulation had a greater effect on overall reaction times than did the eccentricity manipulation. Therefore the magnitude of the CUD is not simply proportional to the overall reaction time. Interhemispheric transmission was probably occurring along visual pathways that are more sensitive to stimulus eccentricity than to intensity. As all of the cortical commissures have been transected surgically in the commissurotomized patients tested, subcortical commissures are probably responsible for the CUD in N.G. and A.A. Unit recordings within the superior colliculus of the monkey demonstrate a retinotopic organization (Schiller and Koerner, 1971; Goldberg and Wurtz, 1972), which may account for the eccentricity effect in N.G. and A.A. As this region receives both retinal and visual cortical neural inputs (Sprague *et al.*, 1973), hypothetically there are at least two neural routes that could account for the visual transfer. The first is a direct ipsilateral visual projection in which midline transfer, presumably via the superior colliculi, occurs before cortical processing. The second possible route involves an interhemispheric subcallosal pathway, in which sensory articulation is reached in the contralateral cerebral hemisphere prior to subcortical transfer. A third, motor, route is discussed below. These pathways are schematically depicted in fig. 3.

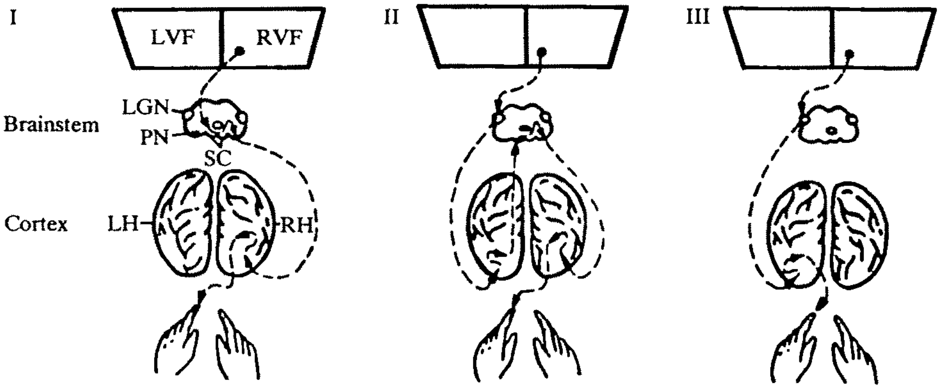

FIG. 3. Schematic representations of theoretical crossed visual-motor connections in patients with complete cerebral commissurotomy during the condition of a left hand response to a light flash presented in the right visual hemifield (RVF). I. Ipsilateral visual system. II. Interhemispheric brainstem route. III. Ipsilateral motor pathway. LVF = left visual hemifield; LGN = lateral geniculate nucleus; PN = pulvinar nucleus; SC = superior colliculi; LH = left cerebral hemisphere; RH = right cerebral hemisphere.

The brainstem visual system may also be important for 'blindsight', in which patients with striate lesions demonstrate visual perceptual abilities in the blind field in the absence of visual awareness (*see* Weiskrantz, 1986, for review). Under forced-choice conditions, patients with scotomas can, to a surprising extent, localize light flashes presented within their blind field (Pöppel *et al.*, 1973; Weiskrantz *et al.*, 1974). Furthermore, hemidecorticated patients can often localize light flashes presented in their hemianopic field (Perenin and Jeannerod, 1978). Monkeys with lesions of the striate cortex can detect light flashes presented in their scotoma, and this ability is lost following lesions of the superior colliculus (Mohler and Wurtz, 1977). As visual association areas in the cortex receive inputs from the superior colliculus via the pulvinar, the entire colliculo-thalamo-extrastriate system is probably important for blindsight abilities (*see* Bruce *et al.*, 1986; Weiskrantz, 1986).

Patients with blindsight presumably have the ipsilateral visual pathway available to them and yet they report that they are not 'aware' of having seen the visual stimuli. By contrast, the commissurotomized patients were fully aware of the presence of light flashes presented in either visual hemifield. Hence response with awareness, as occurs in the commissurotomized patients, could not use only an ipsilateral visual pathway. Furthermore, unlike the blindsight patients, the commissurotomized patients have intact striate cortices. Thus, striate cortical processing appears to be necessary before full cognitive awareness of a visual stimulus can be achieved, and before a response can be freely initiated. Commissurotomized patients N.G. and A.A. are therefore probably responding in the crossed condition by means of a subcortical interhemispheric route, rather than an ipsilateral visual pathway. Moreover, the corticofugal projections to the superior colliculus are probably retinotopically organized (Kawamura *et al.*, 1974; Updyke, 1977), possibly accounting for the eccentricity effect in these commissurotomized patients.

An idiosyncratic pattern of results was obtained from commissurotomized patient R.Y. Despite R.Y.'s understanding that a response was to be made on every trial, he often failed to respond during right visual hemifield presentations with left hand responding (RVF-Lh). This was evident in Experiment 2 for stimuli presented at 4° eccentricity, but not at 10°, and also for Experiment 1 in which all of the stimuli were presented at 4° eccentricity. R.Y. also demonstrated an effect of eccentricity on the CUD, although eccentricity had no effect on the RVF-Lh condition.

R.Y. was the only subject whose CUD was significantly affected by changes in stimulus light intensity. The CUD was paradoxically 38 ms *larger* for bright than for dim light flashes, because of unusual responses in the RVF-Lh condition. Reaction times were significantly *longer* for bright than for dim light flashes during the RVF-Lh condition, while the reverse was true (reaction times were longer for dim stimuli) for all other Hand × Visual Hemifield conditions in Experiment 1. Therefore both the accuracy and the reaction time data suggest an asymmetry in interhemispheric subcortical transfer in this patient. We speculate that there is a lesion, not visualized by MRI, within R.Y.'s left visual association area, which affects the transfer of visual information from the left cerebral hemisphere to the right cerebral hemisphere. The lesion could not be in the geniculostriate pathway into the left hemisphere because right hand responses to the same stimuli are normal. As the deficit appears to occur for stimuli at 4°, but not 10° eccentricity, the damage may be in a retinotopically organized region. The intensity effect suggests that the part of the pathway that is affected precedes subcortical interhemispheric transfer because the CUDs of N.G. and A.A., which presumably represent subcortical interhemispheric transfer, were unaffected by intensity. Thus the paradoxical increase in latency with brighter stimuli in R.Y. may be attributable to greater activation of this malfunctioning system.

For commissurotomized patient L.B., neither intensity nor eccentricity manipulations significantly affected the CUD. Therefore, unlike the other commissurotomized patients, subcortical interhemispheric transfer of visual information is probably not responsible for the CUD. L.B. may be responding in the crossed condition by means of ipsilateral corticospinal motor pathways, that are not quite as effective as the contralateral connections (fig. 3). Compared with other commissurotomized patients, he appears to have unusually effective ipsilateral motor control of both hands (Bogen, 1969; Sperry *et al.*, 1969; Zaidel and Sperry, 1977).

In the boy with callosal agenesis (M.M.) the 12 and 20 ms CUDs fell between the values of the normal subjects and the commissurotomized patients, and were comparable to CUDs of other acallosal patients. His abnormal CUDs are unlikely to be related to his dyslexia or age, as other dyslexic children of his age do not show such sizeable CUDs (Broman *et al.*, 1985). The intermediate CUD values of acallosal patients may represent transfer time across the anterior commissure. However, the CUDs of 2 other acallosal patients varied inversely with increases in stimulus light intensity (Milner, 1982; Milner *et al.*, 1985), whereas M.M.'s CUDs remained invariant either to changes in the intensity or eccentricity of the light stimulus. Individual differences in cerebral neural organization may account for this discrepancy. There is extensive dilatation of the posterior and inferior horns of the lateral ventricles in M.M. As the anterior commissure apparently interconnects visual association area in the temporal lobe, these fibres may be absent or under-represented due to hydrocephalus, precluding anterior commissural transfer of visual information. Alternatively, early neural reorganization may have included the development of relatively effective ipsilateral motor control, as is assumed in commissurotomized patient L.B. In this view, M.M's CUD may be smaller than that of L.B. because ipsilateral motor control would have developed earlier, and hence would be more efficacious, in the acallosal boy.

The following information processing model is proposed to account for the apparent variety of interhemispheric transfer routes. Visual information reaches both hemispheres through direct contralateral as well as indirect ipsilateral projections. However, full awareness of a visual stimulus can only be achieved via the contralateral visual system. Moreover, visual information transfers interhemispherically across the corpus callosum, anterior commissure, and subcortical commissures. Following visual analysis, information undergoes cognitive elaboration, and again abstract cognitive information transfers, perhaps across more anterior parts of the corpus callosum. Finally, information flows into the motor programming stage and motor commands can again transfer between the two hemispheres via cortical and/or subcortical commissures. In addition, each hemisphere has direct contralateral and indirect ipsilateral motor control systems.

In this model, all possible connections are activated simultaneously and result in multiple parallel processes often terminated horse-race fashion by the one that completes processing first. Sometimes priority is established by control from above, rather than by speed. Moreover, response may be delayed until several parallel processes are completed and their results compared.

The model assumes modularity. Thus visual parameters such as intensity, eccentricity, and visual complexity should affect only visual transfer. Furthermore, transfer along a particular visual pathway may be sensitive to one visual parameter (e.g., eccentricity) but not another (e.g., intensity). Similarly, decision complexity should affect the transfer of cognitive/abstract information, but not visual or motor transfer, whereas the complexity of the motor response pattern should affect motor transfer exclusively. Variants of the simple reaction time task that manipulate decision and motor complexity, in addition to visual complexity, should answer some of the questions raised in this paper. Of course it is possible that modularity does not always occur. Then visual parameters may affect decision or even motor transfer, and later stages of processing may affect earlier stages through feedback loops.

The present results from commissurotomized subjects suggest that midbrain commissural fibres transfer information related to the spatial positioning of a stimulus, whereas previous evidence from acallosal subjects indicate that the anterior commissure transfers information associated with stimulus light flux. Similar tests in patients with selective lesions of the corpus callosum (e.g., the splenium versus the body of the corpus callosum), and patients with complete forebrain commissurotomy sparing the anterior commissure, would further clarify the functions of the cerebral commissures.

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SPATIAL AND TEMPORAL CONTRAST SENSITIVITY IN HEMIANOPIA

A COMPARATIVE STUDY OF THE SIGHTED AND BLIND HEMIFIELDS

by R. F. HESS *and* J. S. POINTER

(*From the Physiological Laboratory, University of Cambridge, Cambridge, UK*)

SUMMARY

Spatial and temporal contrast sensitivity was measured, under identical test conditions using spatially and temporally localized stimuli, in 4 normally sighted human subjects and in 3 healthy hemianopic subjects whose stable visual field loss exhibited foveal sparing. Testing was undertaken at central fixation and at a variety of eccentric loci along the horizontal meridian of the sighted and perimetrically blind field. In comparison with the normal (control) sensitivities obtained in this study, spatial and temporal sensitivities in the sighted hemifield in subjects with striate cortical lesions were both reduced; in addition, we were unable to demonstrate greater-than-chance performance at any extrafoveal locations in the blind hemifield.

INTRODUCTION

Recently there has been renewed interest in the possibility of human patients with perimetrically-blind hemifields exhibiting residual vision (Campion *et al.*, 1983). Such spared or residual visual function could arise for several different reasons. One of the more interesting suggestions is that this facility might be due to the participation of subcortical visual projections which are obscured in normal vision by the dominant cortical projection (Sprague, 1966; Schneider, 1969). It was this idea that motivated us to undertake the present study: we wished to define the spatial and temporal properties of any residual vision so that it could then be compared with the available neurophysiological data on the corresponding properties of cells recorded at subcortical sites in the mammalian visual system (Maffei and Fiorentini, 1973).

Consequently we expressly set out to use stimuli for which we have physiological information and for which the physiologically relevant parameters could be controlled (Enroth-Cugell and Robson, 1966; Maffei and Fiorentini, 1973; Derrington and Lennie, 1984). Our stimuli were modulated equally above and below a mean level. This ensured that contrast could be varied within physiological limits

Correspondence to: Dr R. F. Hess, The Physiological Laboratory, University of Cambridge, Downing Street, Cambridge CB2 3EG, UK.

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without modulating light adaptation. This approach also ensured that light scatter to more distal regions was minimal. Secondly, the form of stimulation that we employed was sinusoidal in space and time. This not only permitted accurate control over the spatial and temporal frequency of the stimulus to be detected but also enabled us to explore residual vision that might occupy only a small or discrete region of the spatiotemporal range of normal vision. Thirdly, the stimulus was well localized in space and time by means of Gaussian envelopes. This vignetting ensured that discrete regions of the visual field could be investigated with stimuli whose spatial and temporal properties were well localized. Fourthly, a number of increasingly eccentric visual field loci were investigated, in case any residual vision varied with eccentricity (e.g., due to a peripheral field bias in the subcortical projection). Lastly, we employed temporal two-alternative forced-choice psychophysical testing procedures to obtain criterion-free estimates of detection performance. In using this approach it must be emphasized that we did not specifically set out to investigate the phenomenon of 'blindsight' which has been demonstrated with stimuli and methods that are different from ours (involving unconscious responses, i.e., eye movements) but rather to measure the characteristics of any residual visual function as manifested in an area of the perimetrically-blind visual field using standard psychophysical means which involve conscious responses.

Our experimental approach was to select a small number of hemianopic subjects and to undertake detailed psychophysical investigation on them (*see* Shallice, 1979). In selecting patients we sought to obtain people with stable hemianopic losses arising from different aetiologies with varying times since onset. For example, 1 of our patients had had the field defect since childhood, whereas the other 2 acquired it in adult life.

The results show that using well localized spatiotemporal stimuli we could not find any residual vision at any visual field locus in any of our hemianopic subjects. Unexpectedly we found that the spatial and the temporal contrast sensitivities were impaired across the sighted visual field of all 3 patients.

METHODS

Control subjects

Four normally-sighted healthy human subjects provided control data for these psychophysical experiments. Author J.S.P., a fully optically-corrected myope, was 1 subject, the other 3 being emmetropic individuals. The dominant eye alone of each subject was used for threshold determinations, Snellen acuity being 6/5 in all 4 cases; the nondominant eye was fully covered with an opaque occluder during data collection, and natural pupils were retained. The 3 volunteers were inexperienced in psychophysical procedures and were naive to the aims and purpose of the experiment.

Hemianopic subjects

Three healthy individuals, each with an homonymous hemianopic visual field defect (with foveal sparing) participated in this study. Their relevant clinical details are summarized in the Table. All

TABLE CLINICAL DETAILS OF THE HEMIANOPIC SUBJECTS

Case	*Sex*	*Age (yrs)*	*Time since lesion (yrs)*	*Visual field defect*	*Aetiology*	*Correction for refractive error*	*Snellen acuity*
1 (E.C.)	F	55	2.5	L lateral homonymous hemianopia with macular sparing (2°) (some useful vision in L inferior octant, adjacent to midline)	R cerebral haemorrhage	R $\bar{3}.25/\bar{1}.50 \times 100$ L $\bar{2}.75/\bar{1}.00 \times 80$	6/5 6/5
2 (C.MacD.)	F	25	25	L lateral homonymous hemianopia with macular sparing (2°); scotoma stable > 7 yrs	R subarachnoid haemorrhage (neonatal?)	R $\bar{0}.25/\bar{0}.75 \times 160$ L $\bar{0}.50/\bar{0}.75 \times 55$	6/5 6/5
3 (G.Y.)	M	30	22	R lateral homonymous hemianopia with macular sparing (2°); scotoma stable > 21 yrs	L hemisphere damage (road traffic accident)	R $\bar{0}.25/\bar{0}.25 \times 90$ L $\bar{0}.25$ sphere	6/6 6/6

Case	*Colour vision (100-hue)*	*Ocular motility (in sighted hemifield)*	*Pupil reflexes*	*Ocular pathology*	*Abnormal neurological signs*
1 (E.C.)	Normal	Full	Intact, equal and brisk	Absent	None: normal cognition, attention, memory and speech
2 (C.MacD.)	Normal	Full	Intact, equal and brisk	Absent	None: normal cognition, attention, memory and speech
3 (G.Y.)	Normal	Full	Intact, equal and brisk	Absent	None: normal cognition, attention, memory and speech

3 subjects had normal colour vision (100 hue test), ocular motility and pupillary reflexes. They had no ocular pathology or abnormal neurological signs. Cognition, attention, memory and speech were normal. The extent of their sighted hemifields, as determined using kinetic quantitative perimetry on the Goldmann perimeter (Model 940-K7), are displayed in fig. 1. All subjects were alert and intelligent, with no evident neuropsychological deficits (aphasic or memory disorders): this latter point was especially relevant in connection with the successful operation of our psychophysical test procedure, which employed a two-temporal interval forced-choice paradigm (*see* below, under Procedures). The stable hemifield defect was the only remaining clinical sign of brain damage, computerized tomographic (CT) x-ray scans having indicated that the damage arising from the geniculocalcarine lesion mainly involved the striate cortex (examples given in fig. 2). Subject G.Y. has participated in several vision experiments in other laboratories and his visual deficit has been documented (Barbur *et al.*; 1980); the remaining 2 subjects were completely inexperienced in psychophysical test procedures. Informed consent was obtained from all subjects, hemianopes and controls, before commencement of the sequence of noninvasive psychophysical experiments.

Apparatus

All stimuli were generated and presented, and responses collected and analysed, using a PDP 11/34A laboratory computer. The stimuli were presented in the centre of a Joyce Electronics (Cambridge, UK) raster display (white P4 phosphor) via a Cambridge Electronics Design CED 502 interface system. The mean screen luminance was 100 cd/m^2 and the frame rate was 200 Hz. The contrast linearity of the display screen was measured and found to hold up to 98% contrast. The test room received solely artificial illumination.

Stimuli

Two varieties of visual stimuli were employed: spatial (structured) and temporal (unstructured) displays. The former comprised horizontally-orientated sinusoidal gratings within the spatial frequency range 0.2–30 c/deg (all generated in cosine phase), presented as one-dimensional patterns counterphasing at either 1 or 15 Hz. The latter (flicker) stimuli were produced by contrast reversal of a very low spatial frequency grating (0.01 c/deg) at temporal frequencies within the range 1–32 Hz. For the field size used this amounted to uniform field flicker stimulation. Stimulus contrast was modulated sinusoidally in time and for either stimulus type contrast detection thresholds were measured at central (foveal) and horizontally eccentric retinal locations.

The contrast of each stimulus was weighted with Gaussian functions of space and time (x,y,t). This ensured that the stimuli were well localized spatially and temporally and, by eliminating edge transients, thus ensured that eccentric detection was not differentially biased to the edge of the stimulus proximal to the fovea.

The luminance distribution of each stimulus was specified by

$$L(x,y,t) = L_0[1 + CG(x,y,t) \,.\, \sin(2\pi f_x x) \,.\, \cos(2\pi f_t t)] \qquad (1)$$

where L_0 indicates the space-averaged luminance, C the contrast variable, and f_x and f_t the spatial and temporal frequencies, respectively. The window (spread) function was given by

$$G(x,y,t) = \exp[-(x/S_x)^2 - (y/S_y)^2 - (t/S_t)^2]$$

The term 'spread' signifies the distance in time or space wherein the Gaussian falls from 1 to 1/e (about 0.37). The overall spread function is the product of the horizontal, vertical and time Gaussians, having spreads $S_x = S_y = 2°$ for these experiments, and the temporal spread was maintained at $S_t = 250$ ms; each was truncated at plus and minus 2 spreads.

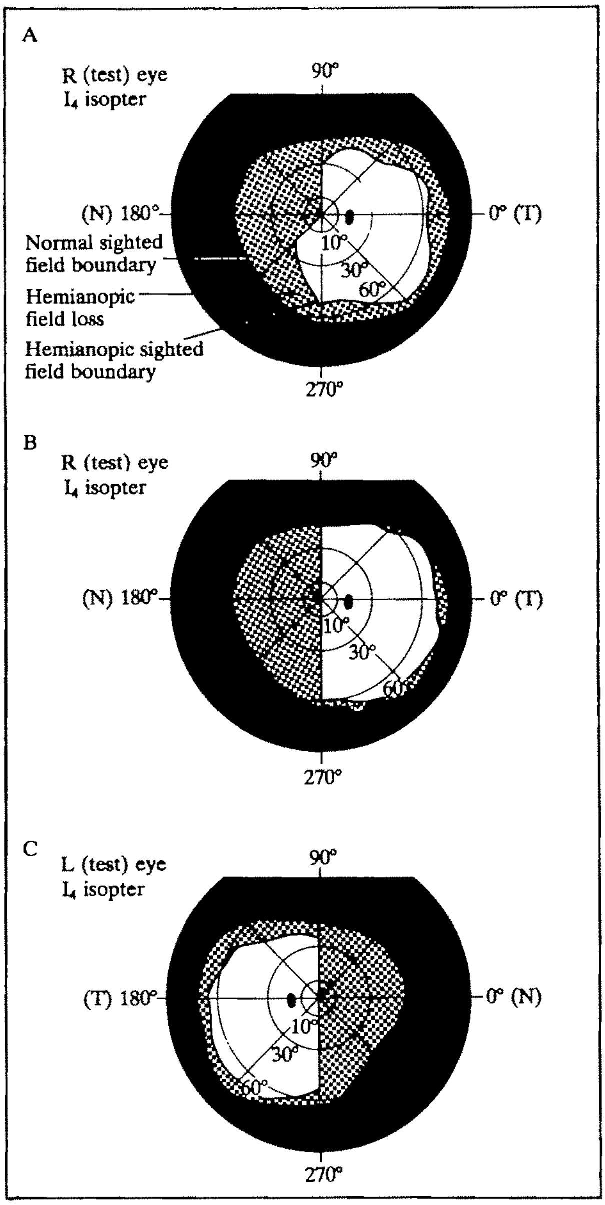

FIG. 1. Visual field plots for white targets (I_4). Right or left (i.e., test) eye of 3 hemianopic subjects with foveal sparing. A, *Case 1*; B, *Case 2*; C, *Case 3*. For comparison, the field boundary (and location of the physiological blind spot) for the right or left eye of normally-sighted naive control subject P.B. is indicated on each plot as the total area within the solid black mask. The stippled area thus indicates the hemianopic field loss. Nasal (N) and temporal (T) fields are identified and the four cardinal meridians are marked. 10, 30, 60 and 90° (outermost circle) eccentricities from central fixation are indicated. Kinetic quantitative perimetry was performed using the Goldmann perimeter (Model 940-K7: Haag-Streit Ag., Switzerland). The instrument was calibrated in accordance with the manufacturer's instructions before each examination. On the particular instrument used here, maximum illuminance at the stimulus was 1,072 lux, i.e., a target luminance of 750 asb or 240 cd/m^2.

General procedures

The display screen was mounted at eye level in a fixed location immediately in front of the subject, and was aligned on his test eye. The display screen was surrounded by a large luminance-matched field which subtended 80° horizontally × 40° vertically at the maximum viewing distance of 3.7 m. A fixation light of adjustable intensity was used to direct the subject's fixation so that horizontally-eccentric visual field locations could be tested.

Testing the sighted field

Monocular photopic contrast detection thresholds were measured for both the structured and for the flickering stimuli, which were varied in spatial or temporal frequency, respectively. A temporal, two-alternative, forced-choice (2-AFC) technique, with feedback, was employed to minimize subjective test bias: the interactive staircase procedure was driven by the subject's responses and controlled by computer. Each trial consisted of 2 presentations (denoted by auditory tones), 1 of which contained the stimulus while the other was a blank field of the same space-averaged luminance. Presentation time was brief ($S_t = 250$ ms), in an attempt to minimize the influence on thresholds of any saccadic eye movements and Troxler's (1804) peripheral fading phenomenon. By contrast, decision time was unlimited but was rarely more than 3-5 s in practice. Immediately after a response had been made, the next two-interval trial started, stimulus contrast being the variable between trials. The average of 6 reversals of the staircase constituted 1 mean. Spatial contrast sensitivity was assessed at 2 loci, centrally (0°) and in the midperiphery (2°), under 2 temporal conditions (1 and 15 Hz). Temporal contrast sensitivity was assessed at 6 loci, centrally (0°) and at 5, 10, 20, 40 and 60° in the near, mid and far-periphery of the horizontal field. Each datum point displayed in the figures herein (expressed as 'contrast sensitivity', the reciprocal of the contrast detection threshold) comprises the arithmetical average of at least two means.

Testing the blind field

A residual visual capacity has been claimed to be present—essentially on the basis of greater-than-chance performance on a variety of visual tasks—in the perimetrically-blind fields of some patients with cortical lesions. The phenomenon has been thoroughly discussed in open forum 'commentary and response' format in conjunction with a review prepared by Campion *et al.* (1983). We chose to investigate the perimetrically-blind hemifields of our patient group using a low spatial frequency flickering stimulus (producing effectively a uniform field flicker). Probability of detection was determined using a frequency of seeing (FOS) 2-AFC psychophysical test paradigm. At each of 6 eccentricities along the horizontal meridian (0, 5, 10, 20, 40, 60°, i.e., the same loci as examined in the sighted hemifield) and for selected test temporal frequencies (within the range 1-32 Hz), a sequence comprising 100 successive trials was presented: each trial consisted of 2 intervals (indicated by auditory tones), one of which contained the flickering stimulus while the other was a blank field of the same space-averaged luminance. The patient's task was merely to indicate by way of a button press in which interval the stimulus occurred. The patient did not need to 'see' the stimulus or know what it was for we did not require it to be correctly identified; the task was simply one of 'detecting something'. Feedback was usually given as to the correctness or otherwise of the response. This was not crucial for the results presented here; similar results were found when feedback was not

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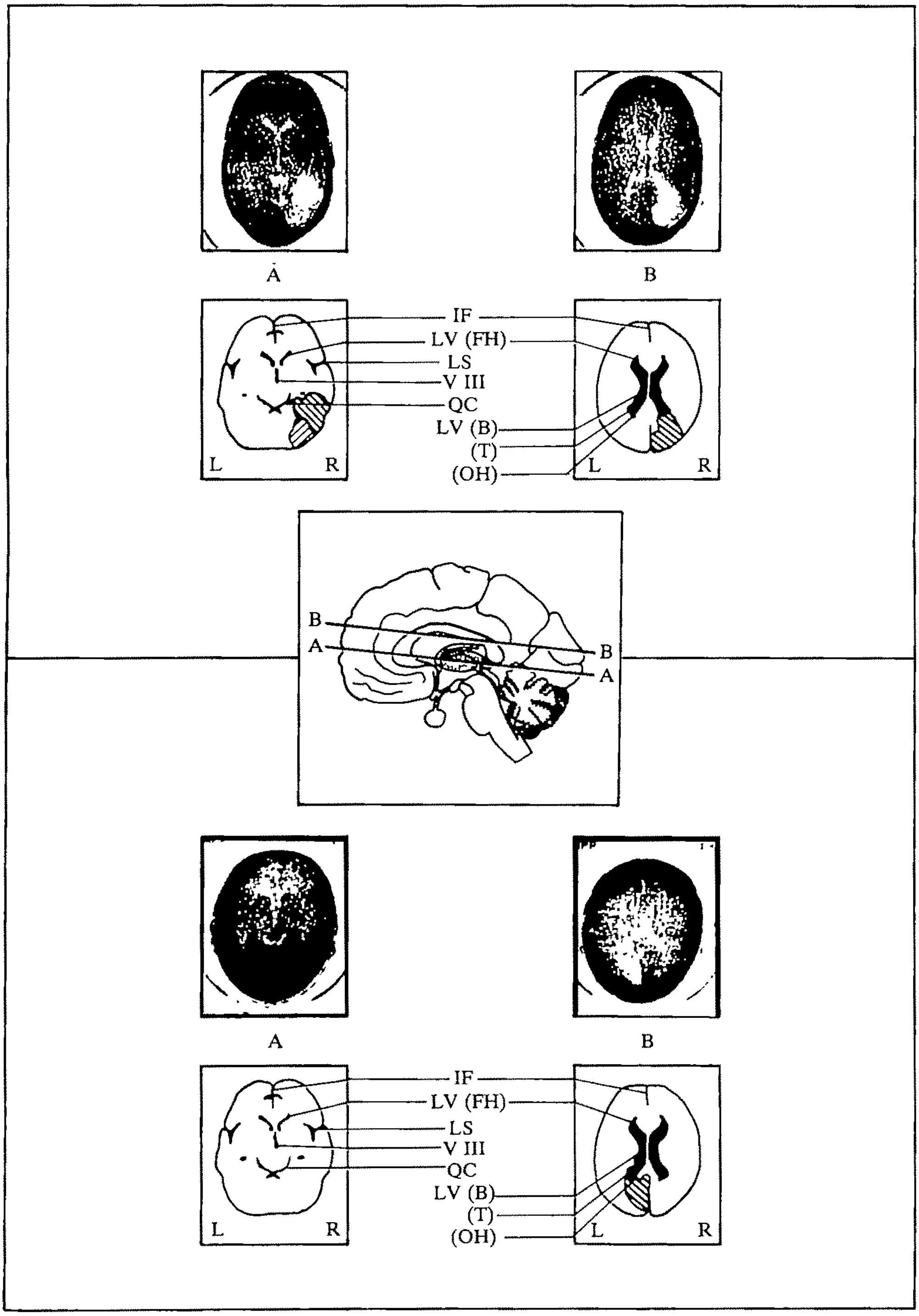
FIG. 2. Unenhanced reversed-contrast CT brain scans and schematic line drawings of hemianopic *Case 2* (in *upper* part: right-sided damage) and *Case 3* (in *lower* part: left-sided damage). The locations of the two sectional planes A and B are indicated on the inset diagram of the medial surface of the brain: plane A is at the low ventricular level and plane B is at the high ventricular level. In the line drawings the ventricles are indicated in solid black, marked hypodensities by dark grey hatching and slight hypodensities by light grey hatching. (Scans of *Case 1* were not available for reproduction here.) IF = interhemispheric fissure; L = left side; LS = lateral sulcus; LV = lateral ventricle—B, body, FH, frontal (anterior) horn, OH, occipital (posterior) horn, T, trigone (atrium); QC = quandrigeminal cistern; R = rightside; V III, third ventricle.


A
B
IF
LV (FH)
LS
V III
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LV (B)
(T)
(OH)
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A
B
IF
LV (FH)
LS
V III
QC
LV (B)
(T)
(OH)
L
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given. Presentation time was brief ($S_t = 250$ ms) but well outside any critical integration time for low level vision. Stimulus contrast remained fixed at a number of preset values over the 100 trials, and on completion of the sequence the percentage correct result was calculated. Up to 6 levels of contrast were tested in this manner for each temporal frequency. The lowest contrast to be tested was determined by the detection threshold found at a similar eccentricity in the sighted field for the same temporal modulation frequency—between 3 and 5 dB of signal attenuation were subtracted from this threshold value to produce the minimum test contrast; the highest test contrast was always set to 90% (1 dB attenuation), and a maximum of 4 further contrast levels were tested between these two extremes. Two, or rarely 3, contrast levels were interleaved in any one run, and each individual FOS datum point displayed in the figures herein usually comprises the averaged results of 2 × 100 trial sequences undertaken on separate occasions.

RESULTS

Control subjects

Normal spatial contrast sensitivity

Spatial contrast sensitivity functions, averaged over $n = 4$ subjects, are displayed in fig. 3 for central (open symbols) and 20° eccentric (filled symbols) viewing, under conditions of slow (1 Hz: fig. 3A) and more rapid (15 Hz: fig. 3B) stimulus contrast modulation. The data of individual subjects over the spatial frequency range tested were not statistically significantly different (three-way analysis of variance (ANOVA), 2 × 2 × 4 factorial design: $F = 0.02$, $df = 3/256$, $P > 0.75$) at either counterphase modulation rate ($F = 0.55$, $df = 1/256$, $P > 0.25$); consequently the mean ($n = 4$) data points are plotted and ±1 SD is indicated. Such consistency amongst individuals is not unusual in human or primate contrast

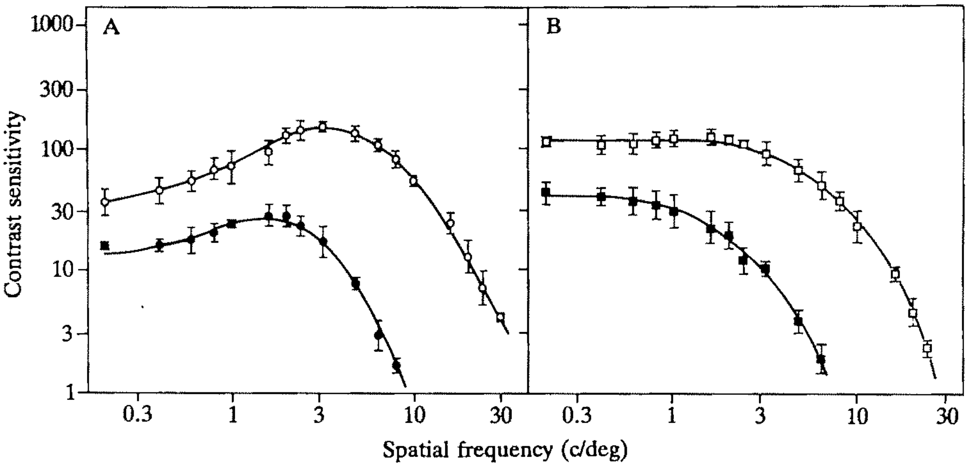

FIG. 3. Spatial contrast sensitivity functions (contrast sensitivity is the reciprocal of the contrast threshold) averaged over the normally-sighted (control) subjects. Each datum point indicates the mean result of independent determinations on 4 subjects; the vertical error bars indicate ±1 SD. Open symbols indicate results for central (0°) fixation, filled symbols results for eccentric (20°) fixation (nasal field). A, results for 1 Hz counterphase stimulation; B, results for 15 Hz counterphase stimulation.

sensitivity determinations (Miller *et al.*, 1980). However, for the group there was a statistically significant difference (F = 126.87, df = 1/256, $P < 0.001$) between central and eccentric thresholds for a given spatiotemporal combination.

The form of these spatial contrast sensitivity data shows (1) foveally, the expected transition from band-pass filter characteristics at a slow contrast modulation rate to the low-pass appearance at an elevated rate (Robson, 1966), and (2) eccentrically, the attenuated but essentially similar form of response across the spatial frequency range when identical spatial test stimuli are used at central and peripheral visual field loci without recourse to spatial 'M-scaling', that is, by not taking into account the cortical magnification factor M (*see* Pointer, 1986, section IX).

Normal temporal contrast sensitivity

Temporal contrast sensitivity functions, averaged over n = 4 subjects, are displayed on three-dimensional coordinates in fig. 4 for each of the 6 visual field test loci. The date of individual subjects over the temporal frequency range

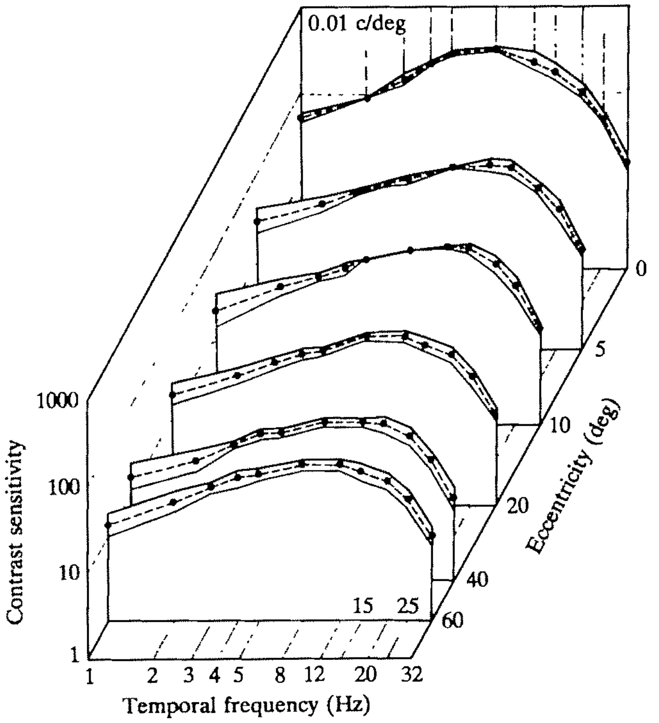

FIG. 4. Temporal contrast sensitivity functions averaged over the normally-sighted (control) subjects. The data are displayed on three-dimensional coordinates, with the 6 independent test eccentricities ranged in sequence along the Z-axis. Results for central (0°) fixation are shown at the rear and those for the greatest test eccentricity (60°) at the front of the figure. Each datum point indicates the mean result of independent determinations on 4 subjects; an interrupted line connects mean data points and the area bounded by solid lines indicates ±1 SD for each datum point.

investigated were not statistically significantly different (two-way ANOVA 4 × 6 factorial design; F = 2.16, df = 3/240, $P > 0.05$) at any given eccentricity; consequently for each test locus an interrupted line connects mean data points, and the area bounded by solid lines above and below indicates ±1 SD. A consistent and statistically significant (F = 17.01, df = 5/240, $P < 0.001$) superiority of central (0°) over peripheral temporal contrast sensitivity was recorded: a post hoc statistical comparison of means (Tukey, 1973) undertaken on these data indicated an honestly significant difference (HSD) between the central (0°) and the 5 peripheral data values (HSD = 4.51, df = 240, $P < 0.01$), although there was an indication of a possible decrement in sensitivity at the greatest eccentricity tested (60°: $P < 0.01$).

The apparent uniformity of extrafoveal sensitivity to very low (0.01 c/deg) spatial frequency stimuli (producing effectively uniform field flicker stimulation) does not appear to have been remarked upon in the literature.

Hemianopic subjects

The sighted field

Spatial contrast sensitivity. The 3 frames of fig. 5 display the foveal (open symbols) and 20° eccentric (filled symbols) spatial contrast sensitivity data for the individual hemianopic subjects for 1 Hz counterphase stimulation. Fig. 6 illustrates the effect on the same 3 subjects' sensitivity of increasing the stimulus contrast modulation rate to 15 Hz. In both figures the broken-hatched (0°) and hatched (20° eccentric) areas indicate the corresponding distribution of results (±1 SD) as obtained under identical test conditions on the normally-sighted control subjects (i.e., the data displayed in fig. 3A, B).

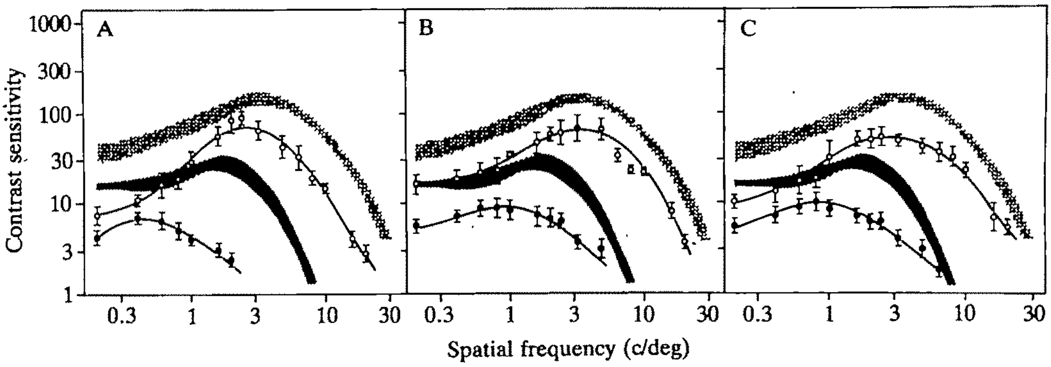

FIG. 5. Spatial contrast sensitivity functions recorded in the sighted hemifield of each of the 3 hemianopic subjects for 1 Hz counterphase stimulation, A, *Case 1*; B, *Case 2*; C, *Case 3*. Open symbols indicate results obtained for central (0°) fixation (all subjects showed foveal sparing of approximately 2°; filled symbols indicate results obtained for 20° eccentric fixation in the sighted hemifield. In all three frames the broken-hatched (0°) and hatched (20° eccentric) areas indicate the corresponding mean control data, ±1 SD, obtained under identical test conditions (i.e., the data displayed in fig. 3A).

The impression that the general form of the contrast sensitivity functions for different hemianopic subjects, under the two test conditions, is similar for the sighted field is confirmed statistically: a comparison of the data of individual subjects (three-way ANOVA, 2 × 2 × 3 factorial design) revealed no statistically significant difference between the hemianopic subjects (F = 0.29, df = 2/192, $P > 0.75$) at either counterphase modulation rate (F = 0.04, df = 1/192, $P > 0.75$). However, again resembling the data obtained from the normally-sighted subjects, there was a consistent statistically significant difference (F = 97.78, df = 1/192, $P < 0.001$) between central and eccentric sensitivity.

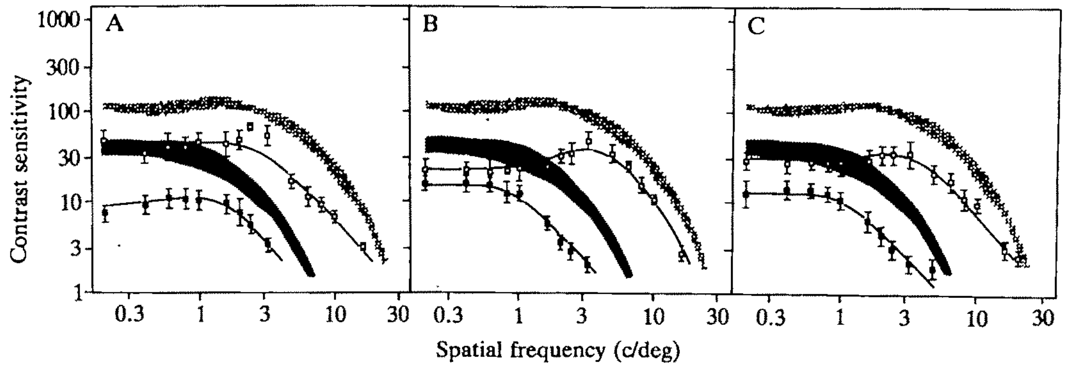

FIG. 6. Spatial contrast sensitivity functions recorded in the sighted hemifield of each of the 3 hemianopic subjects for 15 Hz counterphase stimulation. A, *Case 1*; B, *Case 2*; C, *Case 3*. Results are indicated for central (open symbols) and 20° eccentric (filled symbols) fixation. The broken-hatched (0°) and hatched (20°) areas indicate the mean control data, as displayed in fig. 3B.

The salient feature of these hemianopic-sighted field data is the marked reduction of sensitivity across the entire test spatial frequency range, for each spatiotemporal stimulus and eccentricity, when compared with the data generated under identical test conditions in the normally-sighted control eyes (hatched areas). This feature is statistically significant under all four test conditions: 1 Hz at fovea (Student's t test (two-tailed): t = 2.68, df = 32, $P < 0.02$), 15 Hz at fovea (t = 2.57, df = 30, $P < 0.02$), 1 Hz at 20° eccentricity (t = 3.73, df = 22, $P < 0.01$), 15 Hz at 20° (t = 2.67, df = 20, $P < 0.02$).

The mean reduction of sensitivity for all 3 hemianopic subjects is illustrated in fig. 7 for the 2 contrast modulation rates (compare upper and lower frames) and for the 2 visual field loci (compare left and right-hand frames). In the 4 frames the contrast sensitivity deficit in decibels (dB = 20 log contrast sensitivity) is plotted against spatial frequency. These results were derived by dividing the sensitivity of the mean normal result from fig. 3 by each patient's contrast sensitivity: the means and SDs resulting from this manipulation for each of a

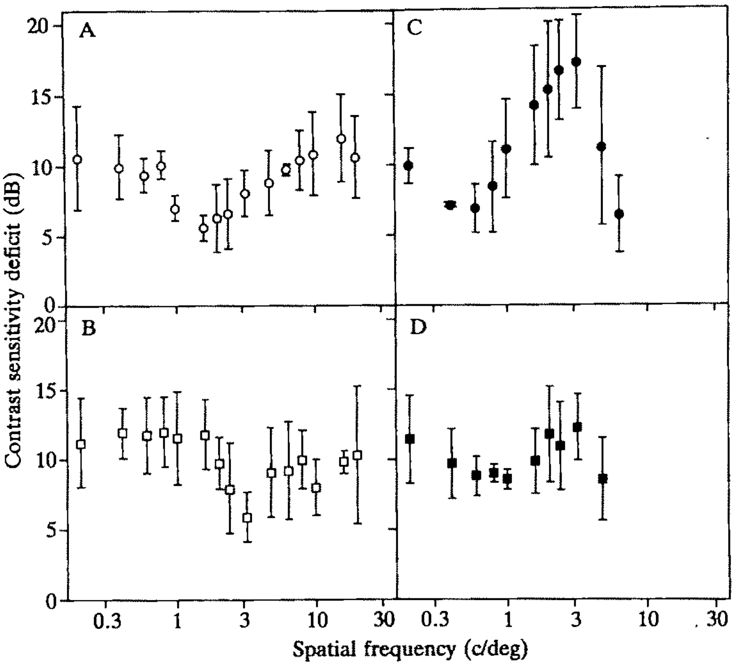

FIG. 7. The ratio of the spatial contrast sensitivity of the normal and hemianopic subjects is displayed for the sighted field of the hemianopic subjects. The *upper* and *lower* frames display results for the two contrast modulation rates (1 and 15 Hz, respectively); the *left* and *right*-hand frames display results for the two visual field test loci (0° and 20°). The sensitivity deficit is indicated along the ordinate in decibel (dB) units; dB = 20 log contrast sensitivity.

number of spatial frequencies are displayed in fig. 7. For the central (0°) fixation (fig. 7A, B) the deficit is very similar for 1 and 15 Hz stimulation. All spatial frequencies are affected although there is an indication that midfrequencies are less affected. For peripheral (20°) fixation again a wide frequency range is involved with the frequency range least affected being lower by a factor of 3.

As a rider to these results it is interesting to note that apparently the perceptual sensation for the hemianope is not of a bisected field but rather of a more generalized slight visual blur, sometimes with an awareness of a shadow in the extreme peripheral field (Bender, 1963). Certainly some patients only realize their field defect when they consistently collide with objects on one side, as was the case for one of our subjects, who had survived the first 17 yrs of life in ignorance of the hemianopic field loss which had arisen in early infancy. The suggestion of a subjective awareness of a slight clouding of vision is significant, as it correlates with the objective finding of depressed contrast sensitivity across the entire spatial frequency range. Indeed one of our hemianopic subjects had mentioned in casual conversation that some years ago it had been suggested that spectacles might be

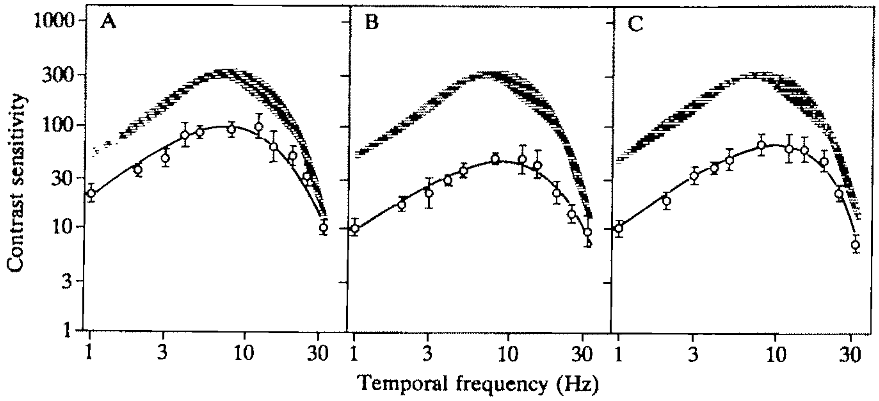

FIG. 8. Temporal contrast sensitivity functions recorded in the sighted hemifield of each of the 3 hemianopic subjects; central (0°) fixation (all subjects showed foveal sparing of approximately 2°. A, *Case 1*; B, *Case 2*; C, *Case 3*. In all three frames the hatched area indicates the corresponding mean control data, ±1 SD, obtained under identical test conditions (i.e., the data displayed in fig. 4).

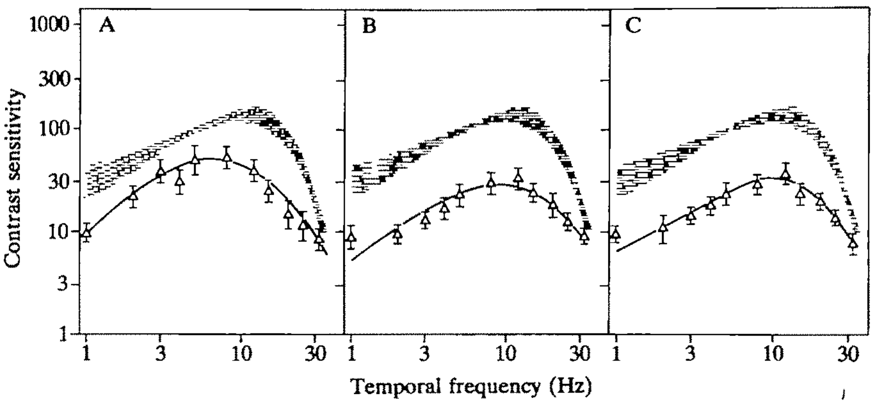

FIG. 9. Temporal contrast sensitivity functions: 5° eccentric fixation in the sighted hemifield (*see* legend to fig. 8 for details). A, *Case 1*; B, *Case 2*; C, *Case 3*.

useful in correcting what was assumed to be a mild degree of myopia: however, a subsequent refraction had indicated no significant refractive error and the 'slight blur' had been tolerated ever since.

Temporal contrast sensitivity. Figs 8–13 display the individual temporal contrast sensitivity functions for each of the six visual field test loci in the sighted field of the hemianopic subjects. In all the figures the hatched area indicates the corresponding distribution of results (±1 SD) obtained under identical test conditions on the normally-sighted control subjects (i.e., the data collectively displayed in fig. 4).

As suggested by the spatial contrast sensitivity data (*see* above), the sighted field of each of our 3 hemianopic subjects exhibits similar sensitivity; over the temporal frequency range investigated, and at any given eccentricity, the data of

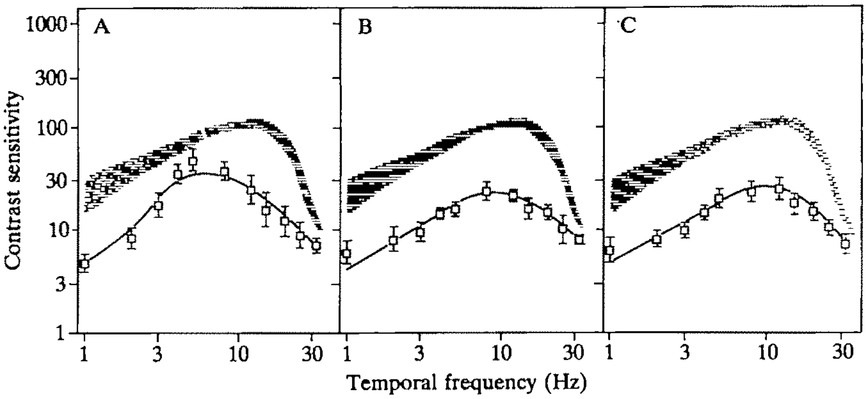

FIG. 10. Temporal contrast sensitivity functions: 10° eccentric fixation in the sighted hemifield (*see* legend to fig. 8 for details). A, *Case 1*; B, *Case 2*; C, *Case 3*.

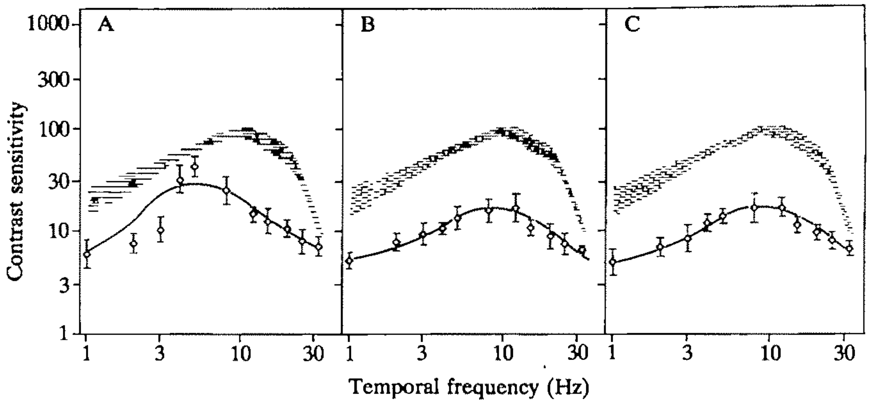

FIG. 11. Temporal contrast sensitivity functions: 20° eccentric fixation in the sighted hemifield (*see* legend to fig. 8 for details). A, *Case 1*; B, *Case 2*; C, *Case 3*.

individual subjects were not statistically significantly different (two-way ANOVA, 3 × 6 factorial design: F = 2.88, df = 2/180, $P > 0.05$). This feature, and the additional statistical confirmation of the superiority of central (0°) over peripheral temporal contrast sensitivity (F = 40.06, df = 5/180, $P < 0.001$) are both in line with the findings on the control subjects (*see* above). However, in a similar manner to the form of the spatial contrast sensitivity data, the hemianopes' temporal contrast sensitivities over the test range are reduced compared with those of the control group. One possible explanation for the foveal results (fig. 8) is that the spared macular region is of lower sensitivity in hemianopia. However, this can offer an explanation only for the foveal decrement in sensitivity in the sighted field. The difference between the two groups (hemianopes vs controls) is statistically significant at each of the 6 test loci: 0° (Student's t test (two-tailed): t = 3.71,

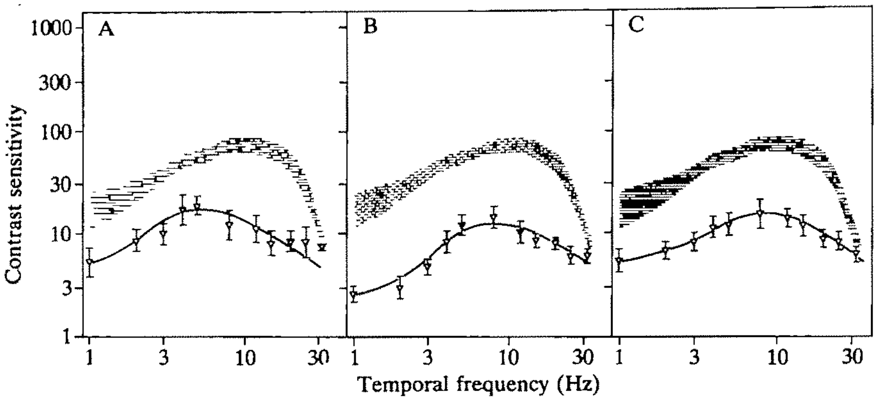

FIG. 12. Temporal contrast sensitivity functions: 40° eccentric fixation in the sighted hemifield (*see* legend to fig. 8 for details). A, *Case 1*; B, *Case 2*; C, *Case 3*.

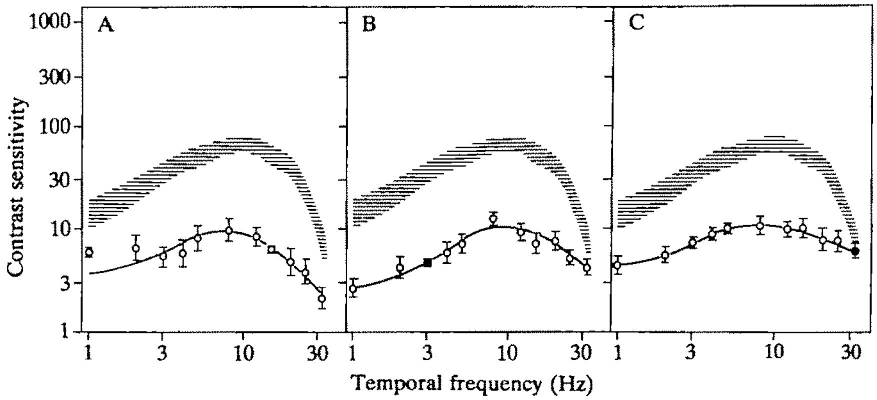

FIG. 13. Temporal contrast sensitivity functions: 60° eccentric fixation in the sighted hemifield (*see* legend to fig. 8 for details). A, *Case 1*; B, *Case 2*; C, *Case 3*.

df = 20, $P < 0.01$), 5° (t = 4.79, df = 20, $P < 0.001$), 10° (t = 5.06, df = 20, $P < 0.001$), 20° (t = 5.91, df = 20, $P < 0.001$), 40° (5 = 6.45, df = 20, $P < 0.001$), 60° (t = 7.62, df = 20, $P < 0.001$).

In a similar manner to the representation of the spatial contrast sensitivity loss, as displayed in fig. 7, the deficit of temporal contrast sensitivity is illustrated in the 6 frames of fig. 14, corresponding to the 6 test loci. The contrast sensitivity deficit in dB is plotted against the temporal frequency of stimulation. These results were derived by dividing the mean normal sensitivity (fig. 4) by each patient's contrast sensitivity. The means and SDs resulting from this procedure are plotted in fig. 14. For central fixation (0°: fig. 14A) the magnitude of the sensitivity deficit in the sighted field of the hemianopic eye is seen to affect a wide range of temporal frequencies and to decrease with increasing temporal frequency. Similar effects

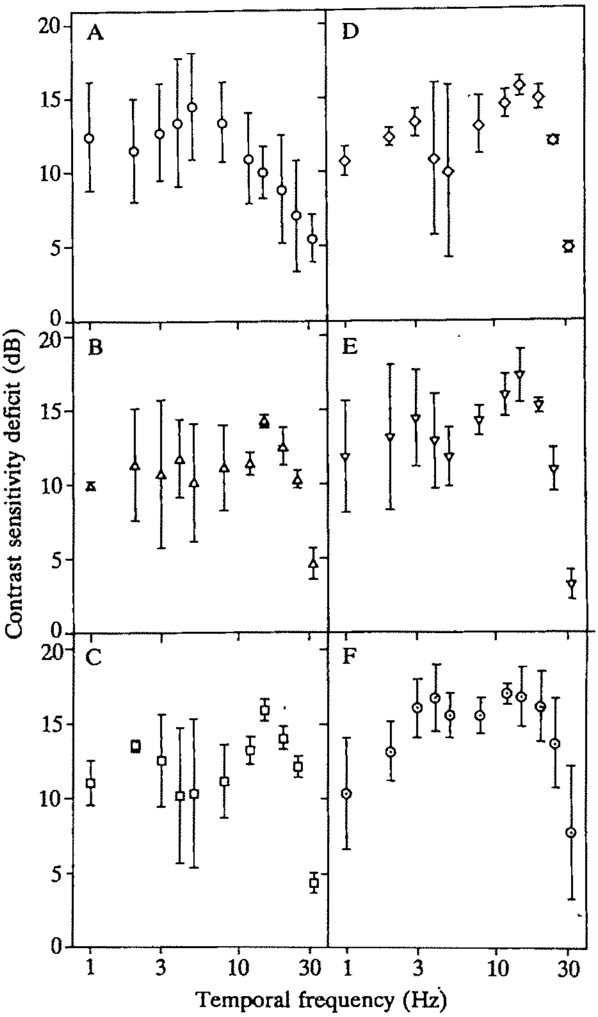

FIG. 14. The ratio of the temporal contrast sensitivity for the normal and hemianopic subjects is displayed for the sighted field of the hemianopic subjects. The 6 frames display results for the central (A) and 5 eccentric visual field test loci: B, 5°; C, 10°; D, 20°; E, 40°; F, 60°. The sensitivity loss is indicated along the ordinate in dB units (*see* fig. 7).

are seen at all peripheral loci tested. This reduction in the deficit at the highest temporal frequency tested is not due to the reduced temporal sensitivity range in the periphery. The results suggest that the temporal contrast sensitivity results in the hemianopic subject group are not well-modelled by a vertical translation down the sensitivity scale of the control subjects' results.

The blind field

Figs 15–19 present data for each of the 3 hemianopic subjects arising from estimates of the probability of detection of the low spatial frequency flickering stimulus. Results shown are restricted to those trials where stimulus contrast was set to its maximum value (i.e., 90% or 1 dB of signal attenuation). This high

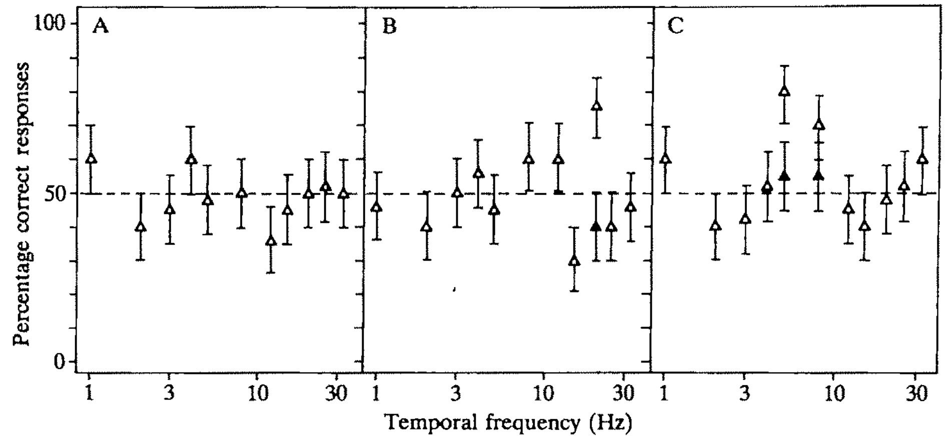

FIG. 15. Frequency of seeing data recorded in the perimetrically-blind hemifield of each of the 3 hemianopic subjects. Eccentric (5°) fixation. A, *Case 1*; B, *Case 2*; C, *Case 3*. Percentage-correct responses are plotted on the ordinate and temporal frequency of modulation along the abscissa. The 50% correct (chance) level is indicated across each frame by an interrupted line. The data displayed are restricted to those trials where stimulus contrast modulation was set to 90% (1 dB of signal attenuation): *see* text for explanation. All subjects showed foveal sparing (approximately 2°), so performance for central fixation was uniformly 100% correct.

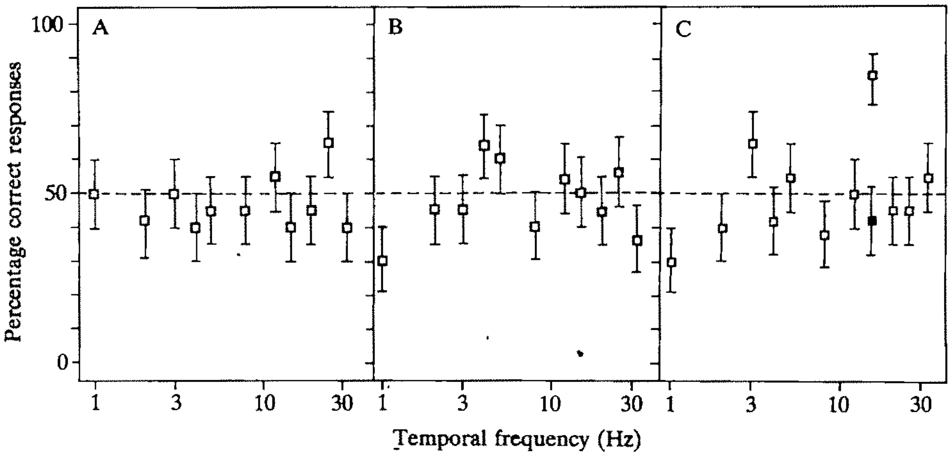

FIG. 16. Frequency of seeing data; 10° eccentric fixation in the perimetrically-blind hemifield (*see* legend to fig. 15 for details). A, *Case 1*; B, *Case 2*; C, *Case 3*.

contrast condition which was just within the linear range of our display screen provided the best possible chance of measuring the spatiotemporal characteristics of any residual vision in the blind hemifield.

These results suggest that performance in the blind hemifield was not consistently above chance (nominally 50% correct: 2-AFC) in any of our subjects at any of the 5 extrafoveal test loci, even for stimuli of maximum contrast. (Since all three subjects manifested foveal sparing, central (0°) performance was 100% correct at

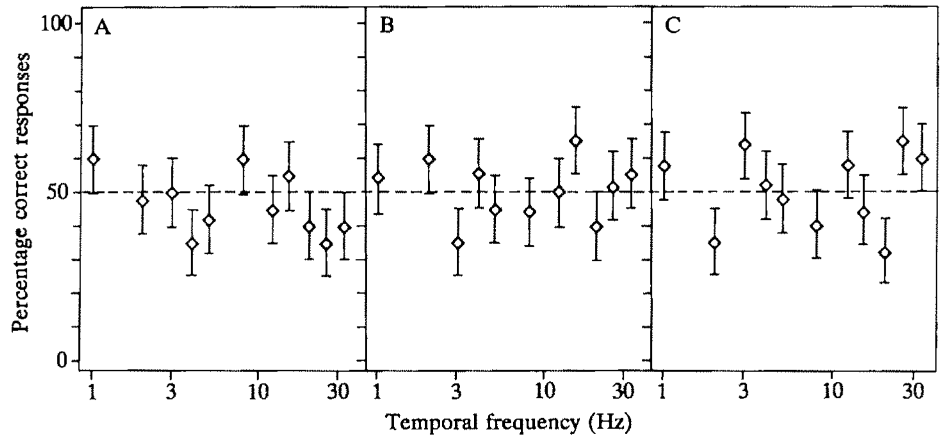

FIG. 17. Frequency of seeing data; 20° eccentric fixation in the perimetrically-blind hemifield (*see* legend to fig. 15 for details). A, *Case 1*; B, *Case 2*; C, *Case 3*.

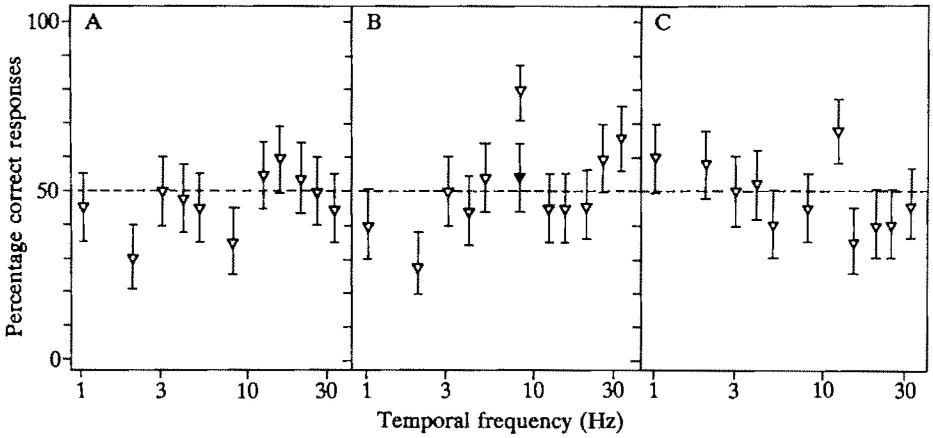

FIG. 18. Frequency of seeing data; 40° eccentric fixation in the perimetrically-blind hemifield (*see* legend to fig. 15 for details). A, *Case 1*; B, *Case 2*; C, *Case 3*.

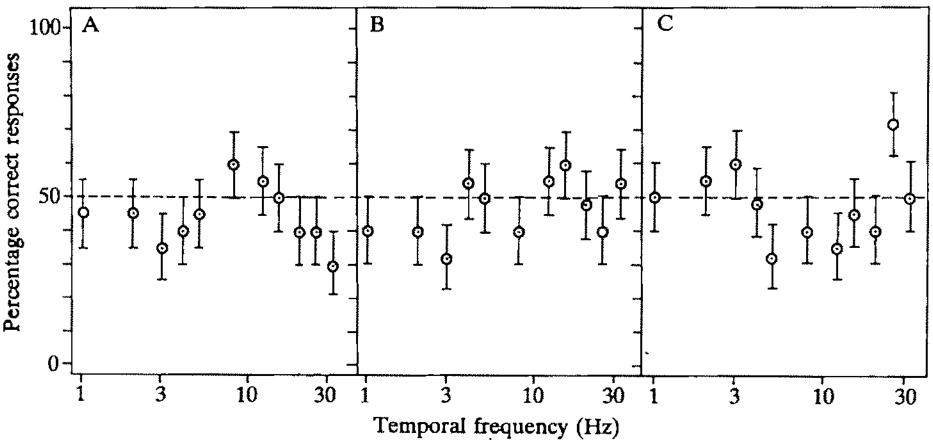

FIG. 19. Frequency of seeing data; 60° eccentric fixation in the perimetrically-blind hemifield (*see* legend to fig. 15 for details). A, *Case 1*; B, *Case 2*; C, *Case 3*.

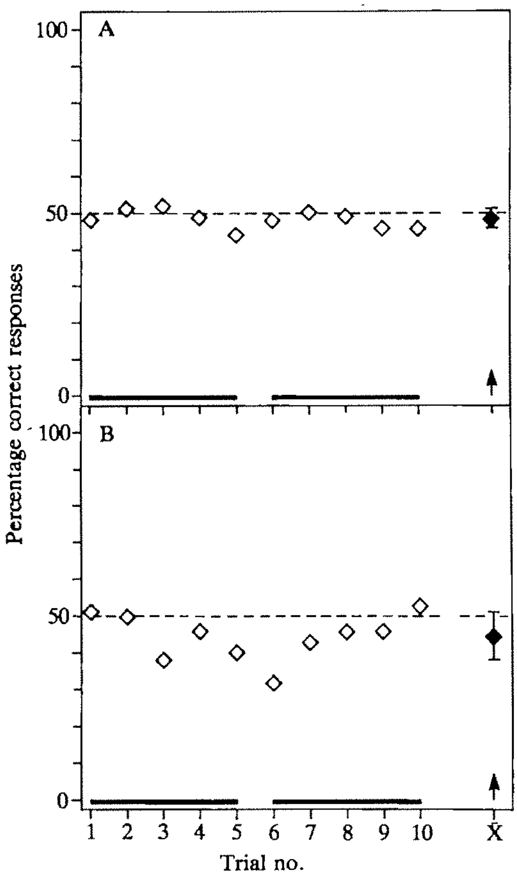

FIG. 20. Result of repeated experimental trials in the perimetrically-blind hemifield of *Case 1*. The data were generated in two series of 5 × 100 frequency of seeing trials at each of two contrast levels. A, results of trials at 90% contrast; B, of trials at 30% contrast. The test location for all trials was 20° eccentric in the perimetrically-blind hemifield. Temporal modulation frequency was 5 Hz, corresponding to this subject's peak modulation response at the same eccentricity in the sighted hemifield (*see* fig. 11A). The isolated datum point indicated by a vertical arrow to the right of the abscissa in both A and B is the mean (±1 SD) of the total of 10 × 100 trials.

90% contrast.) It is true that some isolated readings were significantly above chance but there seemed to be no consistency across temporal frequency or eccentricity. More importantly, these readings were not consistently high when repeated (compare filled with unfilled symbols in figs 15B, C, 16C and 18B).

As a further control, in 1 subject we assessed whether practice might improve performance in the blind hemifield. On two separate occasions subject E.C. undertook two series of 5 blocks of 100 stimulus trials at a locus of 20° in the blind hemifield and at a temporal frequency of 5 Hz (this temporal modulation value producing peak contrast sensitivity for 20° eccentric fixation in the sighted field: *see* fig. 11A). At the first session the sequence of low contrast trials (at 30%) were run before the high contrast (90%) sequence; at the second session later that week the high contrast trials were run first. With reference to the two frames of fig. 20, no consistent trend or improvement in performance with practice was found. The datum point representing the mean of the combined data for the total of 10 × 100 trials is indicated by a vertical arrow to the right of the abscissa in fig. 20A, B.

We deliberately set out to optimize stimulus parameters for testing in the blind field of our subjects. Despite careful attention to spatial frequency, temporal frequency, contrast and visual field test locus using well localized stimuli we could find no evidence of any residual visual function in the perimetrically-blind hemifield of any of our 3 subjects.

It is interesting to note here that these results on patient G.Y. are seemingly at odds with some previous studies on this patient (Barbur *et al.*, 1980; Blythe *et al.*, 1987). One difference between these and the present study concerns the method used for determining threshold. In the present investigation we derived thresholds from the frequency of correct responses in a two-alternative forced-choice procedure whereas in previous studies the patient determined his own threshold using a method of adjustment.

DISCUSSION

Hemianopia: the perimetrically-blind hemifield

Using experimental conditions which would be expected to reveal even the most restricted and rudimentary spatiotemporal visual capacity, we can report no evidence for residual visual function in any region of the perimetrically-blind hemifield of any of our hemianopic patients. This suggests that, contrary to initial expectations, the contrast sensitivity associated with the subcortical projection in man cannot be measured by the standard psychophysical means used in this study. This might be because of the crossed tectal inhibitory effects reported in cat by Sprague (1966) or because the stimuli used here are not optimal for driving subcortical neurons (*see*, e.g., Schiller and Koerner, 1971; Schiller and Stryker, 1972). It should be stressed that our stimuli and methods have been directed towards assessing low level residual vision using a detection threshold procedure and have not been primarily designed to address the issue of 'blindsight' as such.

The residual vision reported by other investigators in the perimetrically-blind hemifield using conscious responses is most probably due to residual cortical function rather than subcortical function. This could be due either to a local sparing of the striate cortex (Pöppel *et al.*, 1973) or to parallel prestriate projections from the thalamus (Benevento and Yoshida, 1981; Fries, 1981; Yukie and Iwai, 1981; Benevento and Standage, 1982; Bullier and Kennedy, 1983; Schiller *et al.*, 1985, 1988). This conclusion does not depend on the time since onset of the defect nor does it depend upon short-term training.

Hemianopia: the sighted hemifield

The finding of reduced sensitivity throughout the normally-sighted hemifield of our hemianopic subjects was unexpected. Although mention of this can be seen in the early literature (*see*, e.g., Battersby, 1951; Teuber *et al.*, 1960; Koerner and Teuber, 1973). The extent to which it was correlated between subjects with very different aetiologies suggests that it is not due to some unrelated, and as yet

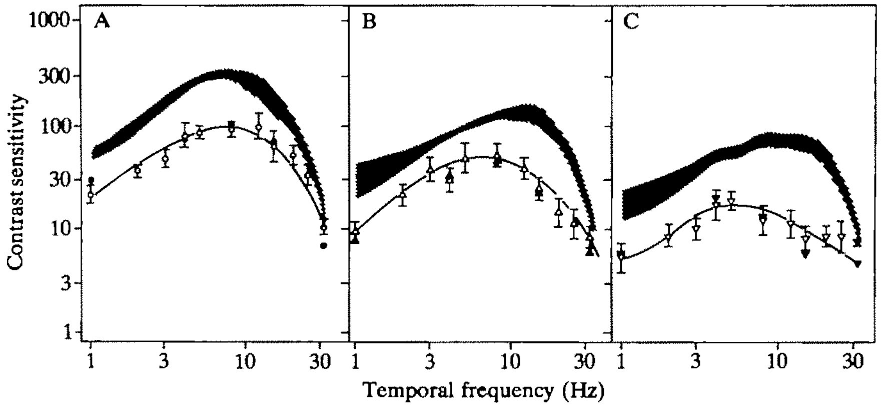

FIG. 21. Temporal contrast sensitivity functions recorded in the sighted hemifields of the right and left eyes of *Case 1*. The right eye was the usual test eye in these experiments: the temporal contrast sensitivity data of this eye are indicated by open symbols and have already been given in frame A of each of figs 8, 9 and 12 for 0°, 5° and 40° eccentric fixation, respectively. The filled symbols included on this composite fig. 21 refer to data collected under identical conditions on the left eye. (For reasons of clarity, ± 1 SD has not been indicated for the left eye data, but was of a similar magnitude to that shown for the right eye.) The hatched area indicates the corresponding mean control data ($n = 4$; ± 1 SD) at the 3 eccentricities (A, 0°; B, 5°; C, 40°) as already shown in figs 8, 9, 12. The similarity of temporal contrast sensitivity in the two eyes across the sighted hemifield is apparent.

undiagnosed, disorder. It appears to be a general phenomenon in hemianopia. Indeed hemianopic subjects are known to complain of blurred vision in the presence of normal visual acuity (Bender, 1963). Since each of our subjects had a defect that was postgeniculate it was unexpected that the visual field ipsilateral to the lesion would be impaired. We have no reason to suspect that the retina was independently affected, because ophthalmological examination revealed no abnormality, pupillary reactions were normal and kinetic perimetry revealed no local abnormalities. Nevertheless, since all these experiments were carried out monocularly it remained a possibility that the hemiretina of the tested eye might be selectively affected. To test this, we compared the temporal contrast sensitivity of the right and left eyes of subject E.C. for stimuli imaged in the sighted field. The results of this check, which are displayed in fig. 21 for 0° (frame A), 5° (B) and 40° (C) eccentricity, show that the reduction in sensitivity in the normally-sighted hemifield is similar, regardless of which eye is tested. This strongly suggests that the deficit has a cortical basis.

There are four remaining possible explanations for this reduction in sensitivity. They are (1) abnormal eye movements, (2) callosal inhibitory influences, (3) incomplete decussation of retinal fibres, and (4) crossed tectal inhibitory influences. Taken in order, abnormal eye movements seem an unlikely possibility. Fixation stability was good and no obvious nystagmus was present; furthermore the loss in sensitivity exhibited broad-band spatial properties and a very extensive visual field distribution. Any explanation involving callosal projections seems equally unlikely firstly because of the extensive distribution of the loss compared with the very localized nature of the callosal projections (Kennedy *et al.*, 1986) and secondly because of the fact that it occurs for stimuli of threshold contrast, whereas recent results in cat and monkey suggest that only high contrast signals are transmitted via this pathway and that as a consequence information is restricted to the low spatiotemporal range (Berardi *et al.*, 1987; Fiorentini *et al.*, 1987). Thirdly, incomplete decussation of retinal fibres is also an unlikely explanation, because the loss of sensitivity was evenly distributed across the visual field yet the decussation of retinal fibres in primates is known to be localized to within a degree or so of the vertical meridian (Bunt *et al.*, 1977; A. Cowey and H. Perry, personal communication).

The last remaining possibility, namely the involvement of crossed tectal inhibitory pathways, seems to be a more likely explanation. Sprague (1966) reported the presence of such crossed tectal inhibitory influences for visually-guided behaviour in cat following unilateral surgical removal of the visual cortex: subsequent removal of the superior colliculus on the side contralateral to the original lesion produced an improved behavioural response to stimuli presented in the previously blind hemifield. A related interhemispheric effect has been also reported in man (Põppel and Richards, 1974) in which a particular visual function can be demonstrated within a major scotoma but only in a position that is mirror symmetric with a small scotoma in the opposite half of the visual field. To explain the present findings one would need to postulate that as a consequence of unilateral cortical damage an ascending tectocortical inhibition occurs on the side ipsilateral to the lesion. This tentative conclusion can only remain one of a number of interesting possibilities until controlled animal experiments can be undertaken. In such future experiments the normally-sighted hemifield should now also be examined. It remains a possibility that the loss of function in the 'sighted field' is due to a much more indirect cause, namely a more diffuse callosal projection or to secondary consequences of retrograde transneuronal degeneration in the retina via, for example, vascular changes.

ACKNOWLEDGEMENTS

We thank all our subjects for their patience in undertaking many hours of experimental work. This study was supported by the UK Medical Research Council under Project Grant No. 8421298/N and by the Wellcome Trust. We also acknowledge useful discussions with Dr W. R. Levick. R.F.H. is a Wellcome Senior Lecturer.

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THE ROLE OF COMPLEMENT IN THE PATHOGENESIS OF EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS

by C. LININGTON,[1] B. P. MORGAN,[2] N. J. SCOLDING,[1] P. WILKINS,[3]
S. PIDDLESDEN[1] *and* D. A. S. COMPSTON[1]

(From the [1]Section of Neurology, Department of Medicine, [2]Department of Medical Biochemistry and [3]Department of Pathology, University of Wales College of Medicine, Cardiff, UK)

SUMMARY

The role of complement in the pathogenesis of demyelination and inflammation has been investigated in a synergistic model of acute experimental allergic encephalomyelitis (EAE) in the Lewis rat. Depletion of serum complement with cobra venom factor (CVF) suppressed the clinical expression of acute inflammatory EAE induced either by immunization with 50 μg guinea pig basic protein (MBP) in Freund's complete adjuvant, or by the passive transfer of 10^7, but not 5×10^7 MBP activated spleen cells. Despite the suppression of clinical disease in actively induced EAE, treatment with CVF only had a significant effect on the severity of CNS inflammation in early disease (12 days postimmunization) when the number of inflammatory foci was reduced by 35%. Three days later this difference had resolved and no significant difference could be detected in the severity of CNS inflammation, although control animals exhibited severe disease, the CVF treated group being clinically normal.

Demyelination in these models is initiated by systemic injection of the antimyelin oligodendrocyte glycoprotein (MOG) monoclonal antibody, 8-18C5, which in vitro lyses oligodendrocytes in a dose, Fc and complement-dependent manner and in vivo induces extensive CNS demyelination in rats with EAE. Treatment with CVF reduced the ability of this antibody to initiate demyelination in vivo and furthermore, its F(ab)2′ fragment had no effect on the clinical course of EAE and was unable to initiate demyelination in normal animals. Complement-dependent mechanisms are therefore involved both in the clinical expression of acute inflammatory lesions and in the pathogenesis of antibody-mediated demyelination in EAE.

INTRODUCTION

Experimental allergic encephalomyelitis (EAE) has been extensively investigated as a model of multiple sclerosis (MS) and a number of studies have indirectly implicated the involvement of complement in the pathogenesis of both diseases. Analyses of cerebrospinal fluid indicate that complement activation occurs within the central nervous system (CNS) in MS (Morgan *et al.*, 1984*a*; Sanders *et al.*, 1986) and both complement (Lumsden, 1971) and terminal component complex

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Correspondence to: Dr C. Linington, Section of Neurology, Department of Medicine, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK.

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(TCC) (Compston *et al.*, 1987) have been demonstrated immunohistochemically in the CNS of MS patients.

Complement is also believed to play an important role in the pathogenesis of antibody-mediated demyelination in chronic relapsing EAE (CREAE) in the guinea pig. CREAE is induced by immunizing juvenile animals with an emulsion of syngeneic spinal cord tissue in Freund's complete adjuvant. Sera from CREAE animals contain a wide spectrum of antimyelin antibodies some of which recognize myelin surface epitopes (Lassmann *et al.*, 1981; Raine *et al.*, 1981; Brosnan *et al.*, 1983; Schwerer *et al.*, 1984; Linington and Lassmann, 1987) and are able to initiate complement-dependent demyelination both in vitro (Dubois-Dalcq *et al.*, 1970; Lebar *et al.*, 1976; Liu *et al.*, 1983; Bradbury *et al.*, 1984) and in vivo (Brosnan *et al.*, 1977; Lassmann *et al.*, 1981). However, humoral immune responses to myelin antigens play little or no part in the pathogenesis of acute EAE which is mediated by an encephalitogenic T cell response (Ortiz-Ortiz and Weigle, 1976; Ben-Nun *et al.*, 1981) and in the rat model, is associated with minimal primary demyelination (Lassmann *et al.*, 1988). In the acute disease, the clinical signs are generally considered to be manifestations of blood-brain barrier dysfunction and CNS oedema (Hirano *et al.*, 1970; Juhler *et al.*, 1984; Kerlero de Rosbo *et al.*, 1985; Goldmuntz *et al.*, 1986; Sedgwick *et al.*, 1987). However, despite this apparent absence of humoral effector mechanisms in acute models of EAE (Seil *et al.*, 1968), depletion of serum complement with cobra venom factor (CVF) can suppress or delay the onset of EAE, without decreasing the extent of CNS inflammation (Levine *et al.*, 1971; Pabst *et al.*, 1971; Morariu and Dalmasso, 1978). These results suggest that serum complement is required for the clinical expression of acute EAE and that clinical disease is not directly mediated by the infiltrating inflammatory cells. Conversely, CVF has no effect on the induction, course or severity of hyperacute EAE in the rat (Levine *et al.*, 1971), and C4 deficient guinea pigs are also susceptible to the disease (Morariu and Dalmasso, 1978).

These conflicting results reflect the difficulties inherent in comparing data obtained using experimental models of EAE which differ significantly in their mode of induction, clinical course and pathological response. Furthermore, the in vivo half-life of the active CVF-factor B complex is short and measurable haemolytic serum complement activity returns after 3–4 days, thereby limiting interpretation of results obtained with this reagent to the acute, predominantly inflammatory phase of EAE.

Recently an acute demyelinating form of EAE has been established in which the significance of complement in the clinical expression and pathogenesis of CNS inflammation and demyelination can be reliably determined (Lassmann *et al.*, 1988; Linington *et al.*, 1988). Intravenous injection of encephalitogenic MBP specific T cells into Lewis rats induces an acute inflammatory response in the CNS and compromises blood-brain function. During this period systemic injection of a CNS myelin specific monoclonal antibody (Mab) 8-18C5 (Linington *et al.*,

1984) results in the formation of large confluent areas of demyelination (Lassmann *et al.*, 1988; Linington *et al.*, 1988). Similar results can also be obtained with this Mab when EAE is actively induced using purified MBP as the encephalitogen (Schluessner *et al.*, 1988).

We have now investigated the requirement for serum complement in the pathogenesis of this synergistic model of acute demyelinating EAE. The results provide evidence that complement is not only involved in the pathogenesis of antibody-mediated demyelination, but that it also plays an important role in the clinical expression of low grade CNS inflammation.

METHODS

Animals and reagents

Lewis rats, weighing 190–220 g were obtained from Bantin and Kingman, UK. Myelin basic protein was purified from whole guinea pig brain and stored lyophilized at −70° C. Cobra venom factor was isolated from lyophilized venom (Naja naja kaouthia, Sigma Chemical Co., Poole, Dorset, UK) by the method of Vogel and Müller-Eberhard (1984). The purified CVF was free of phospholipase A2 activity and was functionally active both in vivo and in vitro. The monoclonal antibody 8-18C5, (specific for the myelin oligodendrocyte glycoprotein (MOG)) and control polyclonal mouse IgG were purified from mouse ascitic fluid and serum respectively, by ammonium sulphate precipitation and ion exchange chromatography (Linington *et al.*, 1988). F(ab)2′ fragments were prepared from purified IgG by pepsin digestion and exhaustive dialysis (Parham, 1986). The purity of these reagents was determined by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) under both reducing and nonreducing conditions (Laemmli, 1970). Enzyme linked immunosorbant assays (ELISA) and Western blotting techniques (Linington and Lassmann, 1987), using antibodies specific for mouse IgG (heavy and light chains) and mouse F(ab)2′, failed to demonstrate intact mouse IgG in the F(ab)2′ preparation, whereas this reagent still reacted with MOG. Normal human serum was obtained from laboratory personnel and was depleted of C9 by passage over a column of monoclonal antihuman C9 antibody coupled to Sepharose 4B (Morgan *et al.*, 1984*b*).

Oligodendrocyte culture

Oligodendrocytes were prepared from the optic nerves of 7 day old Wistar rats (Raff *et al.*, 1983). Cells were cultured on polylysine-coated coverslips in Dulbecco's modified Eagle's medium supplemented with 0.5% fetal calf serum, gentamicin (25 μg/ml), bovine insulin (5.0 μg/ml), human transferrin (100 μg/ml), progesterone (60 ng/ml), putrescine (16 μg/ml), selenium (40 ng/ml), thyroxine (400 ng/ml) and tri-iodothyronine (300 ng/ml). Oligodendrocytes in these cultures were detected by indirect immunofluorescence using mouse monoclonal antibodies specific for galactocerebroside (GC: Ranscht *et al.*, 1982) or MOG (Linington *et al.*, 1984), and polyclonal rabbit antisera specific for MBP (prepared by B.P.M.). Astrocytes were visualized using rabbit antiglial fibrillary acidic protein (GFAP) antiserum (a generous gift from Dr M. L. Cuzner). Appropriate fluorescein and rhodamine antimouse and antirabbit IgG conjugates were purchased from Sigma. Cells were fixed with 2% paraformaldehyde for 15 min followed by 10 s in ethanol/acetic acid (95/5 % v/v) at −20° C to visualize MBP and GFAP. Staining for GC and MOG was performed on live cells at room temperature in the presence of 0.05% sodium azide. The cultures routinely consisted of > 90% oligodendrocytes as determined using these cell markers. Cell viability was determined using propidium iodide and cells examined with a Zeiss universal inverted fluorescence microscope.

Induction of EAE

Active EAE was induced following the injection of 100 μl of a 1:1 emulsion containing 50 μg MBP in phosphate buffered saline (PBS) and 50 μl Freund's complete adjuvant (CFA; Difco) into the hind footpads. Passive transfer of EAE was carried out as previously described (Linington *et al.*, 1988). Rats immunized using the protocol for active EAE were killed at the onset of clinical disease, their spleens removed and single cell suspensions prepared. Spleen cells were cultured for 3 days in RPMI 1640 containing 5% fetal calf serum in the presence of MBP (10 μg/ml) at a density of 2×10^5 leucocytes/ml; cells were collected by centrifugation, washed, counted and resuspended in PBS. Naive syngeneic recipients were then injected in the tail vein with the appropriate number of cells in 1 ml of PBS. All animals were weighed and examined daily for clinical signs of EAE and scored on the scale: 0.5, partial loss of tail tone; 1.0, complete loss of tail tone; 2.0, hindlimb weakness; 3.0, hindlimb paralysis; 4.0, moribund; 5.0, dead.

Rats were decomplemented by intraperitoneal (i.p.) injection of 1 μg/g body wt. purified CVF in Tris-saline. Antibody and F(ab)2′ fragments were administered by injection into the tail vein in 1 ml of PBS.

Animals were prepared for histology by perfusion through the aorta with 4% paraformaldehyde in PBS. Tissue was then immediately removed and fixation continued in the same reagent for 24 h. Tissue was embedded in paraffin and multiple sections cut from various levels of the spinal cord and brain. Sections were stained with haematoxylin-eosin or luxol fast blue in order to assess inflammation and demyelination.

RESULTS

Decomplementation in the Lewis rat by CVF

A single i.p. injection of CVF (1 μg/g body weight) abolished haemolytic serum complement activity for at least 48 h. Low level (0–3% of control) complement activity was detected in the sera of 25% of animals 72 h after injection of CVF. Thereafter, serum haemolytic activity rose slowly reaching 10% of control values by 7 days and was fully restored in all animals 2 weeks after CVF

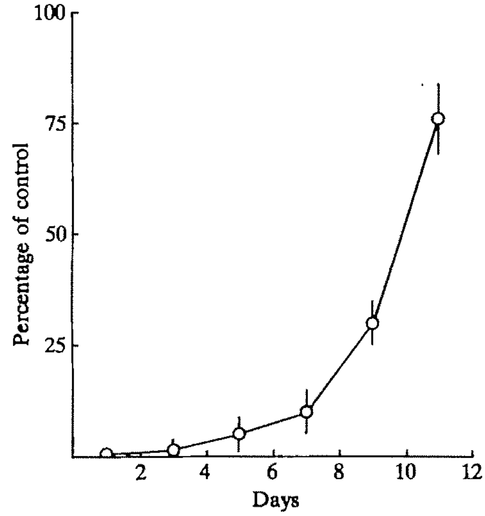

FIG. 1. Effect of a single injection of CVF (1 μg/g body weight) on the serum haemolytic complement activity of Lewis rats (n = 4, error bars denote ±1 SD).

treatment (fig. 1). A second injection of CVF, 4 days after the first, ensured that serum complement activity was completely abolished for a total period of 6 days (data not shown).

Influence of CVF on the course of actively induced EAE

Preliminary experiments confirmed earlier reports (Levine *et al.*, 1971; Pabst *et al.*, 1971) that CVF treatment influences the clinical course of actively induced EAE. Treatment of Lewis rats with CVF on days 0 and 10 after immunization with MBP in CFA entirely abolished the clinical signs of EAE, although in some CVF treated animals recovery of serum complement activity coincided with transient weight loss. In order to avoid the possibility that CVF treatment influenced the development of the encephalitogenic immune response to MBP, the initial CVF injection was subsequently omitted. A single injection of CVF on day 10, 24–48 h before the expected onset of disease, suppressed the development of clinical signs in an experimental group of 10 rats (fig. 2). No clinical evidence of EAE subsequently developed in CVF treated rats studied for up to 30 days postimmunization (p.i.) with MBP/CFA, even though haemolytic serum complement returned to control levels by day 18.

Histological examination revealed that despite the absence of clinical disease, CVF treated animals had extensive perivascular cuffs of inflammatory cells

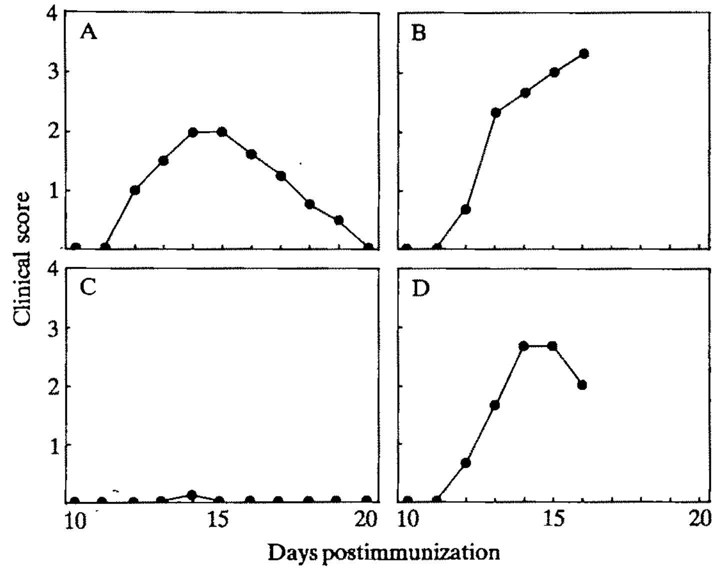

FIG. 2. Influence of CVF treatment on the clinical course of actively induced EAE. EAE was induced with purified MBP. Animals were injected i.p. on day 10 with either Tris/saline (A, n = 8; B, n = 6) or CVF (1 μg/g body weight), (C, n = 10; D, n = 6). The effect of complement depletion on the in vivo activity of the 8-18C5 antibody injected i.v. on day 11 is shown in panels B and D. Controls (panels A and C) received an equivalent dose of polyclonal mouse IgG. In no case was the SEM greater than 20% of the mean clinical score for the control animals between days 10–17 p.i.

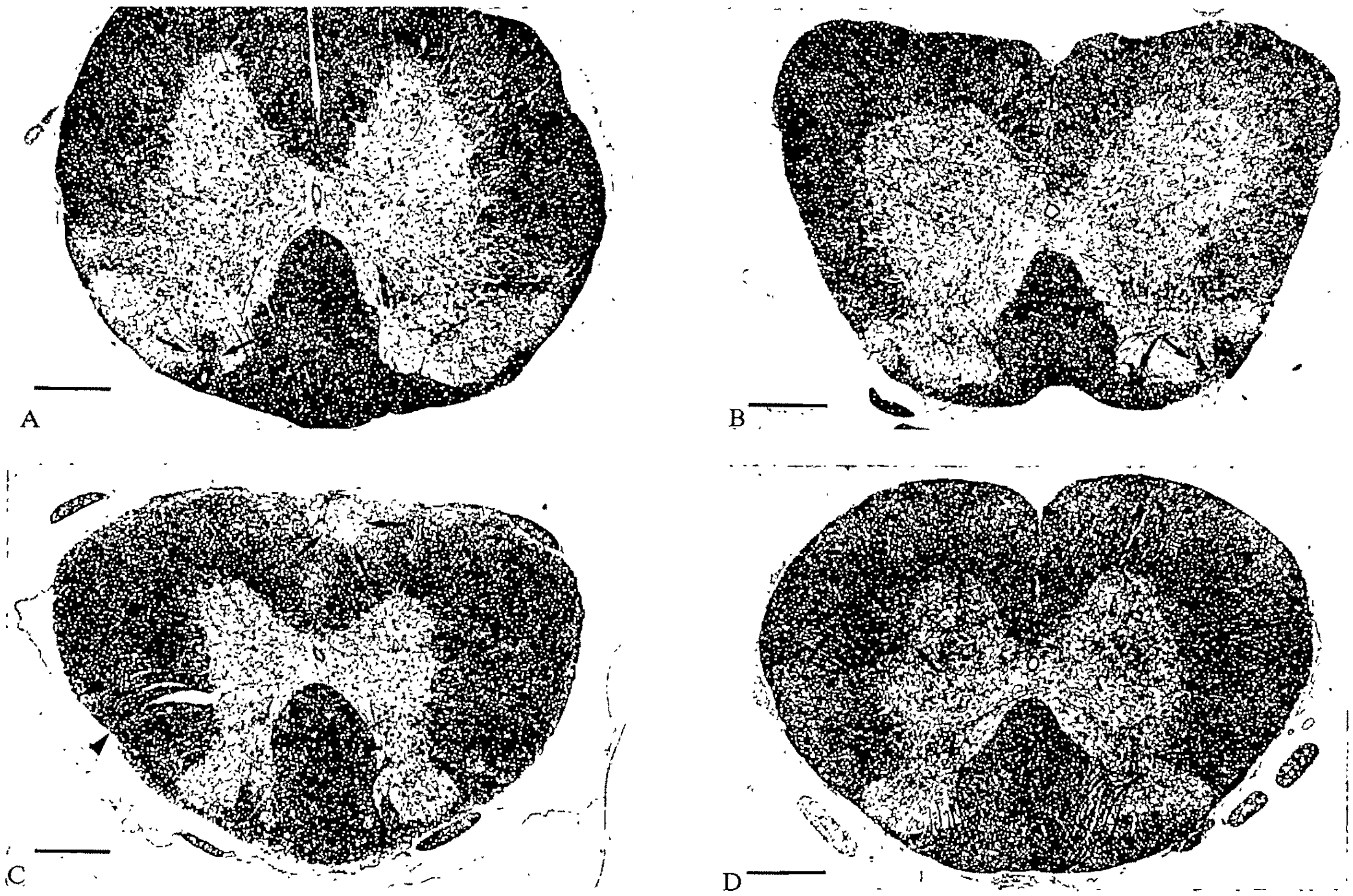

FIG. 3. A, spinal cord section of a rat with actively induced EAE, 15 days p.i. when killed. This animal exhibited severe hindlimb paralysis. B, as in A but treated with CVF 10 days p.i. This animal was clinically well when killed. Note the typical perivascular location of the inflammatory infiltrates in these sections. C, spinal cord section from an animal with actively induced EAE injected i.v. with the 8-18C5 Mab, 15 days p.i. Note the extensive areas of subpial and confluent perivascular myelin loss indicated by the arrow heads. D, as in C, but decomplemented on day 10 p.i. Note the absence of demyelination despite white matter inflammation. Luxol fast blue. Bars 500 μm. E-H on facing page.

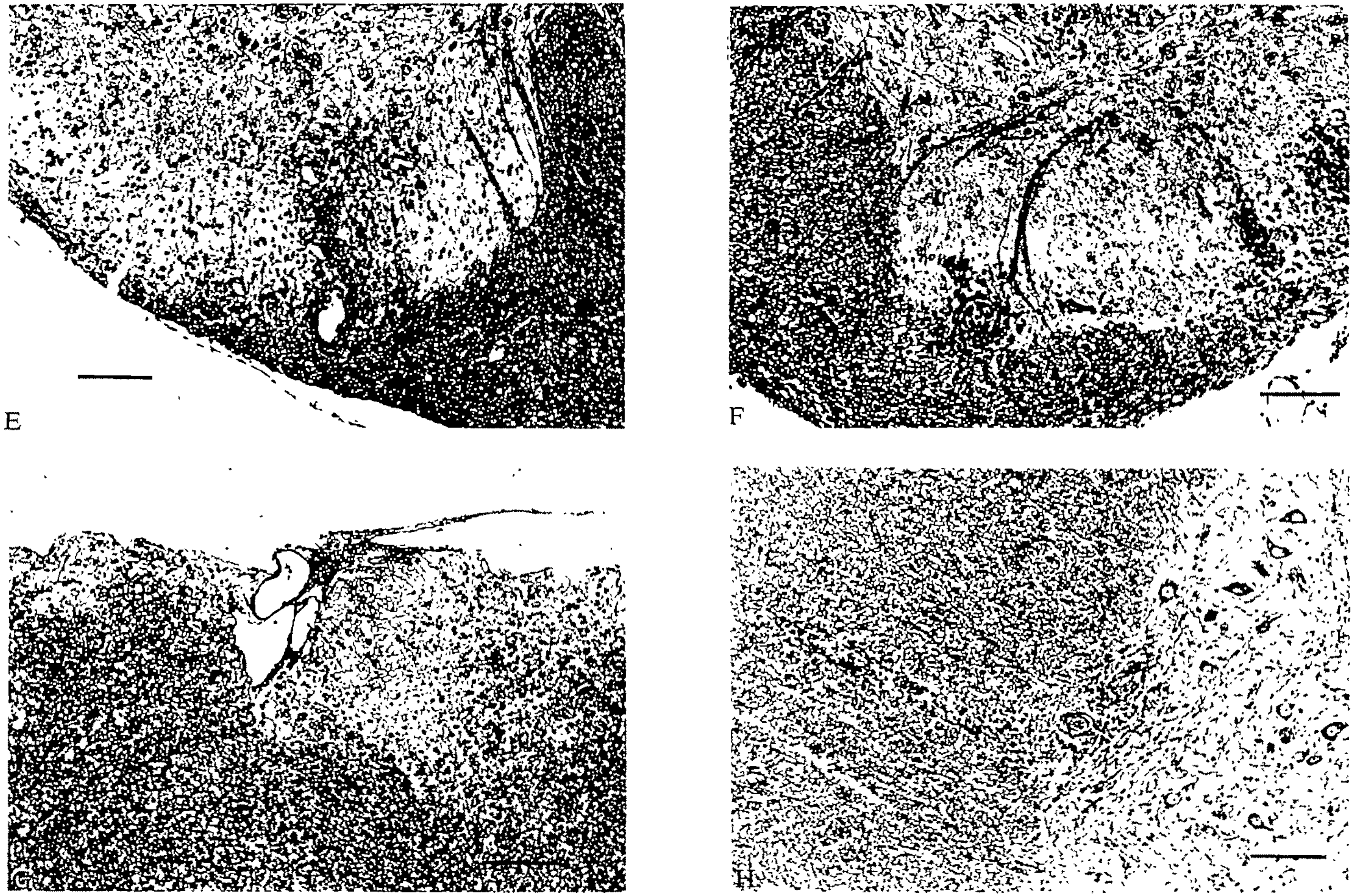

FIG. 3. E–H, higher magnification of the lesions indicated by the arrows in A–D, respectively. Luxol fast blue. Bars 100 μm.

throughout the CNS (fig. 3). Although there were no obvious differences in the intensity, number or distribution of inflammatory infiltrates seen in animals with clinical EAE and those treated with CVF at the height of clinical disease (15 days p.i.), CVF treatment did reduce the number of inflammatory foci present in the lumbar spinal cord by 35% ($P<0.005$) during the onset of clinical disease (12 days p.i.; Table 1). Staining with luxol fast blue revealed no demyelination at the level of resolution obtained in this light microscopic study (fig. 3). These observations indicate that CVF treatment acts to dissociate the clinical and histological signs of EAE.

TABLE 1. THE INFLUENCE OF CVF TREATMENT ON CNS INFLAMMATION DURING THE COURSE OF ACTIVELY INDUCED EAE*

	Number of inflammatory foci/spinal cord section	
	EAE controls (mean ± SD)	*CVF treated (mean ± SD)*
Day 12	8.5±2.6 (n = 4)	5.6±1.7 (n = 4)
Day 15	5.1±3.1 (n = 4)	5.2±3.3 (n = 4)

* Rats with actively induced EAE were perfused with paraformaldehyde both at the onset (day 12 p.i.) and at the height of clinical disease (day 15 p.i., *see* fig. 2). Multiple sections were prepared from the lumbar region of each spinal cord and stained with haematoxylin-eosin. A minimum of 19 sections from each animal were counted in order to determine the mean density of inflammatory foci/spinal cord cross-section. CVF treatment reduced the number of inflammatory foci by 35% ($P<0.005$, Student's t test) at the onset of disease, although there was no significant difference subsequently. As the animals for each time point were taken from different experiments, no significance should be placed on the apparent reduction in the number of infiltrates between days 12 and 15 p.i.

Action of CVF on passively transferred EAE

The effect of CVF treatment was also investigated in a passive transfer model of EAE in which disease was induced by the transfer of activated MBP specific T cell blasts derived from the spleens of MBP immunized rats. This model offers the advantage that activation of the effector T cell population occurs in vitro and cannot therefore be influenced by CVF treatment of the recipients. Furthermore, the clinical severity of the disease was readily manipulated by varying the number of activated spleen cells transferred.

The injection of 10^7 MBP activated spleen cells induced a mild monophasic form of EAE in which animals lost weight and developed hindlimb weakness (fig. 4A). In contrast, injection of 5×10^7 cells/animal resulted in all animals being moribund within 5 days of cell transfer (fig. 4B). The ability of CVF treatment to suppress clinical signs of EAE in this model was dependent on the dose of MBP activated spleen cells used. The milder clinical disease induced with 10^7 spleen cells was suppressed by injection (i.p.) of CVF 24 h after cell transfer (fig. 4C). The onset of clinical disease was delayed in the CVF treated animals and the mean clinical score reduced from 2 (SD = 0) to 0.5 (SD = 0.55, n = 6 for both groups). Once again, despite suppressing clinical disease, CVF had no obvious effect on CNS inflammation in animals examined 5 days after cell transfer. In contrast to these observations, CVF treatment had no effect on severe EAE induced with 5×10^7 spleen cells, even when serum complement activity was further depleted by a second injection of CVF 3 days after cell transfer and 24–48 h before the onset of clinical disease (fig. 4D).

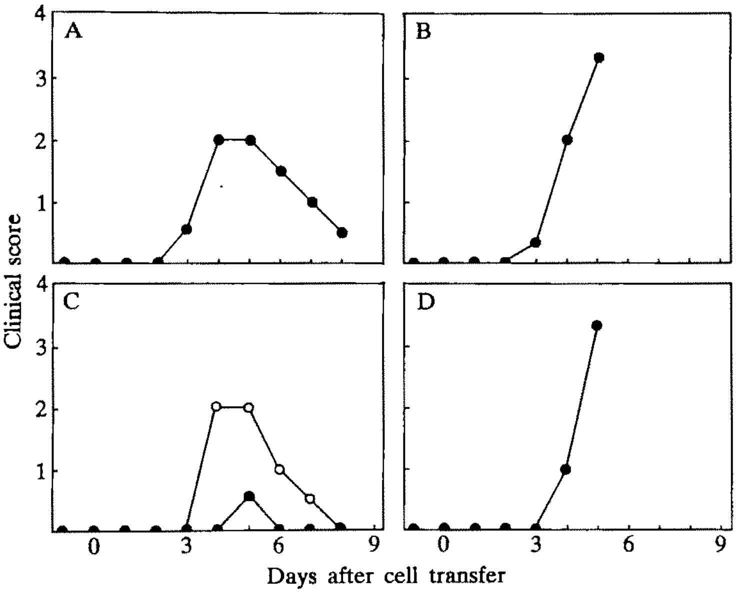

FIG. 4. Influence of CVF treatment on the clinical course of passively induced EAE. EAE was induced by the transfer of either 10^7 (A, C) or 5×10^7 (B, D) MBP activated spleen cells on day 0 (n = 6 in each case). This was followed 24 h later by an i.p. injection either of CVF (C, D) or an equal volume of Tris/saline (A, B). These injections were repeated 72 h later in groups B and D. A further group of animals also received an i.v. injection of 8-18C5 Mab on day 3 (C, n = 4, open circles). The SEM did not exceed 15% of the mean clinical score with the exception of those CVF treated animals with transient disease on day 5 (C, closed circles).

Complement dependent oligodendrocyte lysis by the 8-18C5 Mab in vitro

The mechanism by which the anti-MOG Mab, 8-18C5, mediates demyelination in vivo (Linington *et al.*, 1988) was investigated in vitro. Oligodendrocytes maintained in culture for several days express the MOG epitope recognized by the 8-18C5 Mab on their surface (N.J.S., unpublished results). Addition of varying concentrations of the 8-18C5 Mab to the cultured cells, in the presence of fresh human serum as a source of complement, resulted in a dose dependent lysis of oligodendrocytes. Antibody-mediated damage to the target cells was quantitated by fluorescence microscopy using the criterion of propidium iodide exclusion (fig. 5).

Inactivation of complement either by heating the serum at 56° C for 20 min or depletion of C9 by passage over an anti-C9 antibody column abolished the lytic potential of the Mab, although in the latter case lysis was restored following reconstitution with purified human C9. These experiments demonstrate that the antibody mediates oligodendrocyte damage via the complement cascade, ultimately resulting in the formation of membrane attack complex. This was further demonstrated in experiments using 8-18C5 F(ab)2′. Although the F(ab)2′ fragment bound to the oligodendrocyte surface, determined by fluorescence microscopy, it failed to mediate oligodendrocyte lysis (fig. 5) indicating that lysis is mediated by the Fc C1q binding domain via the classical activation pathway.

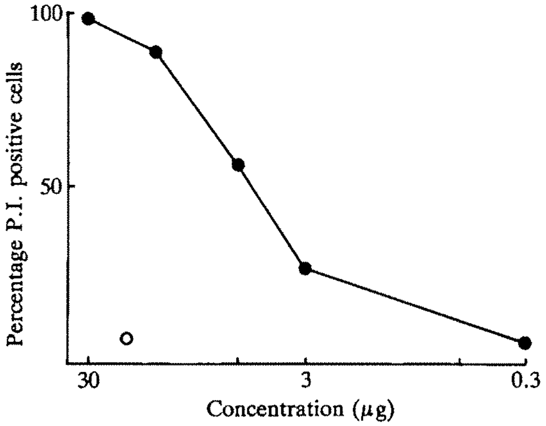

FIG. 5. The myelin/oligodendrocyte glycoprotein-specific monoclonal antibody, 8-18C5, is cytotoxic to cultured oligodendrocytes in vitro. Rat oligodendrocytes were cultured in vitro for 8 days and then incubated with 20% normal human serum in the presence of various dilutions of purified 8-18C5 Mab for 20 min at 37° C, after which propidium iodide (PI) was added and cell permeability determined by fluorescence microscopy (filled circles). F(ab)2′ 8-18C5 fragments failed to lyse oligodendrocytes or increase their permeability to PI (open circle). Results obtained from a representative experiment.

Complement depletion inhibits antibody mediated demyelination in vivo

Previous studies have demonstrated that i.v. injection of the monoclonal antibody 8-18C5 before the onset of both actively and passively induced EAE, increases disease severity and initiates widespread perivascular and subpial demyelination (fig. 3; Schluesener *et al.*, 1987; Lassmann *et al.*, 1988; Linington *et al.*, 1988). We have confirmed these observations and used this model of EAE to determine the role of complement in acute antibody-mediated demyelination in vivo.

Rats (n = 6) were injected with 8-18C5 11 days after sensitization with MBP to induce acute demyelinating EAE (fig. 2B). Although treatment with CVF protected these animals from the potentially lethal effect of the Mab, the antibody did induce clinical disease, that is, loss of weight and tail tone, followed by hind limb paralysis (fig. 2D). Histologically, the induction of clinical signs was associated with demyelination although this was reduced in comparison with animals not treated with CVF (fig. 3).

Similarly, no demyelination was observed in animals with EAE induced with either 10^7 or 5×10^7 MBP sensitized spleen cells and treated both with CVF and 8-18C5 Mab, 3 and 4 days after the cell transfer, respectively. Control CVF treated animals with EAE injected with polyclonal mouse IgG in place of 8-18C5 Mab remained clinically well and exhibited no CNS demyelination.

TABLE 2. COMPARISON OF THE IN VIVO EFFECTS OF THE 8-18C5 ANTIBODY AND ITS F(ab)2′ FRAGMENT ON THE COURSE AND PATHOLOGY OF ADOPTIVELY TRANSFERRED EAE*

Experimental group	*Maximum score*	*Time to maximum score (h)*[a]	*% weight loss*[b]	*Pathology*[c]
EAE controls				
1	2	72	6	I
2	3	72	11	I
3	2	72	9	I
8-18C5				
4	4	24	21	D
5	5	24	18	D
6	5	24	24	D
8-18C5 F(ab)2′				
7	2	72	10	I
8	2	72	12	I
9	2	72	11	I

* Animals were injected with 10^7 MBP activated spleen cells on day 0 followed by (a) 5 mg polyclonal mouse IgG, (b) 5 mg 8-18C5, (c) 4 mg 8-18C5 F(ab)2′ on day 4. Animals injected with either 8-18C5 or its F(ab)2′ fragment in the absence of EAE developed no clinical or histological signs of EAE. [a] From time of antibody injection; [b] determined on day 6; [c] inflammation, D = demyelination.

In addition to using CVF treatment to examine the importance of complement components in this model of antibody-mediated demyelination, we also assessed the ability of 8-18C5 F(ab)2′ fragments to substitute for the intact Mab and initiate demyelination in vivo. In contrast to the intact antibody, injection of 8-18C5 F(ab)2′ into rats with passively transferred EAE (4 mg i.v. at the onset of clinical disease) failed to modify the severity, course or pathology of the disease and did not induce demyelination (Table 2). These results confirm the in vitro study and demonstrate that the Fc region, which contains the C1 binding site, is an absolute requirement for the antibody to initiate demyelination in vivo.

DISCUSSION

In the present study, clinical signs of acute but not hyperacute EAE were suppressed after decomplementation by CVF although CNS inflammation, assessed histologically, was unchanged at the height of clinical disease. In an acute synergistic model of antibody mediated, demyelinating EAE, CVF treatment demonstrated that serum complement is also necessary for antibody-mediated demyelination in vivo.

CVF acts by binding factor B and forming a stable C3 and C5 convertase (CVF-FB), thereby rapidly hydrolyzing these components in an uncontrolled manner and depleting serum of haemolytic complement. A number of short-lived activation products (e.g., C3a, C5a), which mediate a range of biological activities including anaphylaxis and chemotaxis, are generated in this process. However, the half lives of these activation products are short (Jose, 1987) and the rat appears to suffer no immediate or long-term effects from CVF treatment other than a gross depletion of haemolytic serum complement. It is, however, unclear as to how effective CVF treatment is at depleting complement within the CNS. Monocytes have the capacity to synthesize all the complement components necessary for TCC formation (Hetland *et al.*, 1986) and astrocytes have been reported to synthesize C3 and factor B (Lévi-Strauss and Mallat, 1987). It is therefore possible that low levels of complement may be synthesized locally in inflammatory CNS lesions and escape activation by the CVF-FB convertase complex. CVF appears to be effective for 3–4 days in the rat, after which serum complement is again detectable, effectively limiting studies of CVF mediated decomplementation to the acute phase of EAE. Although some complement deficient rat strains are available, they have not been characterized for susceptibility to EAE. We therefore consider that CVF treatment is at present the method of choice for determining the role of complement in the pathogenesis of EAE.

The initial event in the induction of EAE is recognition of the target antigen by activated T cells; this results in blood-brain barrier dysfunction and CNS infiltration by inflammatory cells (*see* Wekerle *et al.*, 1986). In the rat, mild clinical EAE induced either by active immunization with MBP or the transfer of encephalitogenic T cells, is an inflammatory disease without significant demyelination (Lassmann *et al.*, 1988; Linington *et al.*, 1988), in which the clinical signs are believed to depend on blood-brain barrier dysfunction and CNS oedema (Kerlero de Rosbo *et al.*, 1985; Goldmuntz *et al.*, 1986; Sedgwick *et al.*, 1987). Since in EAE, CVF treatment can suppress low grade clinical disease without affecting CNS inflammation, the clinical expression of these inflammatory events within the CNS must involve a complement dependent mechanism which is not directly dependent on the inflammatory infiltrate. This hypothesis is supported by experiments in which severe clinical EAE has been induced in leucopenic rats in the absence of inflammatory cells in the CNS (Sedgwick *et al.*, 1987).

The mechanism by which complement acts to induce the clinical expression of low grade CNS inflammation is uncertain. However, as the encephalitogenic T cell response induces blood-brain barrier dysfunction (Sedgwick *et al.*, 1987), serum complement will gain access to the CNS during acute EAE. In vitro, isolated CNS myelin (Vanguri *et al.*, 1982; Silverman *et al.*, 1984) and more importantly, intact cultured rat oligodendrocytes (N. J. Scolding *et al.*, unpublished results) can activate complement in the absence of myelin specific antibodies. This mechanism, however, does not result in gross demyelination in acute inflammatory EAE (Lassmann *et al.*, 1988; Linington *et al.*, 1988), suggesting that either protection mechanisms act (Ramm *et al.*, 1983; Carney *et al.*, 1985; Morgan *et al.*, 1987) to inhibit complement-mediated demyelination in vivo, or any damage is sublytic. Nevertheless, activation of complement and the deposition of sublytic levels of TCC on the oligodendrocyte/myelin complex may have a direct effect on cell metabolism, stimulating the production and release of leukotriene B_4 by oligodendrocytes (Shirazi *et al.*, 1987). Furthermore, significant amounts of inflammatory mediators such as C3a and C5a would be released, further increasing vascular permeability and stimulating infiltrating inflammatory cells to produce potentially harmful biological compounds (prostaglandins, toxic oxygen metabolites and lysosomal enzymes) (Rother *et al.*, 1985; Jose, 1987). CVF treatment would obviously suppress this response.

Serum complement is not an absolute requirement for the clinical expression of CNS inflammation in EAE. Large doses of encephalitogenic spleen cells override the suppressive effect of CVF and induce severe clinical disease in the absence of normal levels of serum complement. This form of EAE is associated with intense CNS inflammation, in which axonal damage and secondary demyelination are notable features (Lassmann *et al.*, 1988), and it appears to be a better model of acute disseminated encephalomyelitis than MS. The importance of complement-dependent mechanisms for the clinical expression of CNS inflammation therefore appears to be inversely proportional to the severity of the inflammatory insult.

In contrast to its involvement in the inflammatory aspect of EAE, the role of complement in the pathogenesis of acute antibody-mediated demyelination is far clearer. We have formally demonstrated that the monoclonal antibody, 8-18C5 lyses mature oligodendrocytes in vitro in a complement and Fc dependent manner. However, CVF treatment failed to abolish antibody-mediated demyelination completely in vivo. In this situation, demyelination and the associated clinical signs of disease may reflect either opsonization of myelin by antibody followed by Fc receptor-mediated macrophage attack, the activation of complement synthesized locally within the CNS by monocytes or astrocytes, or the biological consequences of C1, C2, C4 activation, as these components of the complement system are unaffected by CVF treatment.

In vivo, demyelination initiated by the 8-18C5 Mab is intimately associated with macrophages (Lassmann *et al.*, 1988; Linington *et al.*, 1988) and, furthermore, depletion of the macrophage population in vivo will suppress EAE and inhibit demyelination (Brosnan *et al.*, 1981). These results indicate that antibody-mediated demyelination in EAE may be initiated by at least two mechanisms, the action of which may be synergistic, namely direct complement-mediated lysis and Fc-mediated macrophage attack. Antibody-dependent complement activation on the myelin surface will release complement derived macrophage activators and opsonize the membrane with C3b, for which macrophages express a specific receptor. In addition, TCC deposition may promote an influx of calcium (*see* Campbell, 1987), activating calcium-dependent phospholipases and neutral proteases (Banik *et al.*, 1985) and inducing vesicular disruption of myelin (Schlaepfer, 1977), thereby destabilizing the membrane and increasing its susceptibility to external attack by macrophage-derived enzymes (Cammer *et al.*, 1986). These mechanisms would account for the patterns of myelin destruction seen in EAE, vesicular dissolution of myelin adjacent to macrophages, invasion of macrophages into myelin sheaths and phagocytosis of myelin debris, sometimes in association with coated pits (Lassmann *et al.*, 1988).

The results of the present study have demonstrated that complement plays an important role in the clinical expression and pathogenesis of both inflammation and demyelination in EAE. However further experiments are required fully to characterize the role of complement in vivo, in particular the relative importance of TCC formation and complement-derived inflammatory mediators, in the complex sequence of events which leads to cellular damage in the CNS and neurological dysfunction in EAE.

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PARAESTHESIAE AND HYPAESTHESIA FOLLOWING PROLONGED HIGH-FREQUENCY STIMULATION OF CUTANEOUS AFFERENTS

by DAVID BURKE *and* CLARA APPLEGATE[1]

(*From the Unit of Clinical Neurophysiology, Department of Neurology, The Prince Henry Hospital and School of Medicine, University of New South Wales, Sydney, Australia*)

SUMMARY

The activity of cutaneous afferents was recorded in human subjects using microelectrodes inserted into individual fascicles of the median nerve at the wrist before and after a 10 min train of electrical stimuli at 200 Hz delivered to the appropriate digital nerve (via ring electrodes) or to individual afferent axons (via the microelectrode). Changes in neural activity produced by the stimulation were correlated with the time course of paraesthesiae and with changes in the ability to detect cutaneous stimuli. From approximately 20 s after the end of the stimulus train, there was a progressive increase in neural activity, and individual afferents became spontaneously active and discharged in high-frequency bursts. At this time the subjects began to experience paraesthesiae. Repetitive stimulation proximal to a complete digital nerve block induced paraesthesiae that were felt distal to the block in the insensate digit, indicating that they did not arise from the unmyelinated terminal segment of the axon or from a stimulus-induced disorder of receptor function. Recordings of the compound action potential evoked by submaximal test stimuli were made after the 10 min stimulus train and revealed evidence of an early transient increase in excitability superimposed on a long-lasting decrease in excitability, reaching a nadir approximately 30–40 min after the end of the repetitive stimulation. In parallel recordings, there was no detectable change in the cutaneous afferent volley evoked by mechanical stimulation of the skin. These findings are consistent with the views that the poststimulation positive symptom, paraesthesiae, can be attributed directly to a disturbance in peripheral afferent fibres, while the poststimulation negative symptoms such as hypaesthesia arise from stimulation-induced refractoriness at central synaptic relays.

INTRODUCTION

Repetitive activity causes an axon to undergo profound long-lasting changes in excitability, the result of active hyperpolarization due to an electrogenic sodium pump and passive depolarization due to extracellular accumulation of potassium (Ritchie and Straub, 1957; Schoepfle and Katholi, 1973; Raymond, 1979;

Correspondence to: Professor David Burke, Unit of Clinical Neurophysiology, The Prince Henry Hospital, P.O. Box 233, Matraville, Sydney, Australia 2036.

[1] Present address: Department of Neurology and Neurological Surgery, Washington University School of Medicine, St Louis, Missouri 63110, USA.

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Kocsis *et al.*, 1983; Barrett and Barrett, 1982; Bostock and Grafe, 1985). In human subjects, repetitive activation of cutaneous afferents at 200 Hz produces changes in excitability dependent on the duration of stimulation: stimulus trains of 1 min duration produce a postactivation decrease in axonal excitability; those of 10 min duration produce a transient increase in axonal excitability superimposed on profound long-lasting subexcitability (Applegate and Burke, 1989), presumably reflecting a shifting balance between the two opposing processes, passive depolarization and active hyperpolarization.

High-frequency repetitive activation of cutaneous afferents at 200 Hz for 10 min is invariably followed by cutaneous sensory symptoms. For some 5 min or more subjects experience paraesthesiae in the distribution of the stimulated nerve (Bergmans, 1970; Ochoa and Torebjörk, 1983; Ng *et al.*, 1987; Applegate and Burke, 1989). In addition, the threshold for perception of mechanical stimuli applied to the skin is increased during and following repetitive stimulation (*see* Bergmans, 1970, 1973; Ng *et al.*, 1987). It is tempting to attribute the paraesthesiae to ectopic impulses generated in axons rendered hyperexcitable by their repetitive activity and the hypaesthesia to the longer-lasting axonal hypoexcitability. However, repetitive stimulation could also have effects peripherally, due to antidromic invasion of receptor terminals, and centrally, due to the high-frequency afferent barrage entering the central nervous system. It is an assumption that the stimulation-induced changes in axonal excitability are responsible for the perceptual disturbances, though it would be consistent with recent microneurographic studies that have specifically correlated axonal activity with the type and intensity of the evoked percept (Ochoa and Torebjörk, 1983; Vallbo *et al.*, 1984; *see also* Konietzny *et al.*, 1981). The techniques used in these studies have, however, been subject to trenchant criticism (Wall and McMahon, 1985) and defence (Torebjörk *et al.*, 1987).

The present experiments were undertaken to determine whether the changes in excitability of cutaneous afferent axons induced by repetitive stimulation contribute directly to the postactivation perceptual disturbances. It was found that the paraesthesiae can be attributed to ectopic impulses in the stimulated axons but that the negative symptoms, hypaesthesia and disturbed sensation, cannot be attributed to axonal hypoexcitability.

METHODS

Twelve experiments were performed on 3 healthy adult volunteers with their informed consent and with the approval of the appropriate institutional ethics committee. The subjects were seated with the relevant forearm and hand resting supine on padded supports on a table. Temperature was monitored using thermocouples on the skin and maintained by blankets and radiant heat.

In 6 experiments, neural recordings were made using sterile insulated tungsten microelectrodes inserted manually into individual cutaneous fascicles of the median nerve at the wrist, much as described by Vallbo *et al.* (1979). At this level, individual nerve fascicles innervate only skin or only muscle. Fascicles innervating digits rather than the palm were specifically sought and the electrode tip was manipulated so that afferents innervating the pulp of the digit dominated the recording. By impaling a nerve fascicle innervating a different digit it was possible to examine poststimulation changes in neural activity more than once in each experiment. Multiunit cutaneous afferent activity was recorded from 7 fascicles following a prolonged train of electrical stimuli delivered to the appropriate digital nerve using ring electrodes around the proximal phalanx. The stimulus train consisted of square-wave pulses (duration 0.1 ms) of constant current delivered at 200 Hz for 10 min using a Grass S88 stimulator with stimulus isolation and constant current units.

In different experimental sequences in the same 6 experiments, poststimulation changes in the activity of 7 single cutaneous afferents were studied. With these single-unit recordings, the stimulus train was delivered through the microelectrode directly to the relevant axon (Ochoa and Torebjörk, 1983) rather than through the ring electrodes, in order to limit the number of axons stimulated and so preserve the signal-to-noise ratio for the single unit. To ensure that the intrafascicular train was of adequate intensity to activate the relevant axon for the duration of the train, the required stimulus level was established as that capable of resetting the discharge of basally active afferents or of producing a poststimulus silent period in the discharge evoked by a repetitive skin stimulus (as in figs 2A and 3A, B). These stimuli were delivered through a preamplifier, with which the recording can be interrupted by a relay for some 10–20 ms at a fixed rate of 1 Hz to allow the delivery of an intrafascicular stimulus (McKeon and Burke, 1980). Stimuli adequate to activate the afferents produced reasonably discrete tactile sensations in the digital skin, overlapping the unit's receptive field. The subject noted the radiating cutaneous sensation when the relevant axon was activated consistently. The recording was then switched off and external stimuli were delivered at 1 Hz through the microelectrode from the Grass S88 stimulator. The stimulus level was increased to reproduce the identical radiating sensation, at which level the stimuli presumably activated the afferent. To ensure that this was so (and that it remained so for the 10 min train) the stimulus level was increased further until it was perceived as more extensive and mildly nociceptive, and repetitive stimulation at 200 Hz for 10 min was then given using this stronger stimulus intensity. It was not the intention of this procedure to stimulate only one axon but to ensure that the stimulus always excited the relevant axon, even if a few adjacent axons also happened to be excited. Inevitably the technique was time-consuming and only stable single-unit recordings survived the procedure and the subsequent stimulus train. To confirm that the same afferents were being studied before and after the stimulus train, the amplitude and morphology of the afferent's spike potential and the site of its cutaneous receptive field were monitored.

With multiunit recordings, the poststimulus changes in axonal excitability were monitored using submaximal test stimuli of constant current delivered through the same ring electrodes as used for the repetitive stimulation, recording the evoked compound sensory action potential through the intrafascicular microelectrode. The intensity of these test stimuli was usually 50% or less of that required to evoke a maximal potential, and the compound sensory action potential was approximately 30–40% of maximal size (*see* fig. 5). These stimuli produced paraesthesiae down the digit, of maximal intensity in the pulp of the finger. In addition, mechanical stimuli were delivered to the pulp of the digit innervated by the fascicle and the naturally evoked afferent volley recorded, care being taken to ensure that both test volleys (electrically evoked and mechanically evoked) sampled the same population of afferents as were activated by the 10 min stimulus train. With 3 fascicles the mechanical stimuli consisted of maintained skin indentation and skin scraping performed manually by the experimenter. With 4 fascicles, the mechanical stimuli were delivered by a Ling-Altec type 201 vibrator, driven by a square-wave pulse to produce a maintained skin indentation lasting 150 ms. To ensure that the application of the percussion head to the skin remained constant the digit was strapped to the frame of the vibrator with the percussion head indenting the skin slightly. The intensity of percussion was limited in order to avoid dislocating the intrafascicular microelectrode, such that the mechanically evoked afferent volleys were submaximal.

The subjects were requested to note any sensory disturbances occurring after cessation of the stimulus train and to signal the intensity and frequency of paraesthesiae both by tapping on a strain gauge and by verbal reports (using a 0–5 scale, corresponding to none, minimal, mild, moderate, strong, very strong). Formal sensory testing was not undertaken during the microneurographic experiments because too many external stimuli might alter the evolution of axonal excitability and the sensory symptoms, and could jeopardize the intrafascicular recording. All neural data were recorded on tape for off-line analysis.

In 3 separate experiments, the ability to detect discrete punctate stimuli was measured using graded von Frey hairs (Semmes-Weinstein Aesthesiometer, Stoelting Co., Chicago) applied single-blind in an unpredictable sequence to a specific site on the pulp of the index finger. The threshold was taken to be the force that could be detected by the subject on 8 out of 10 presentations. Changes in this threshold following repetitive stimulation of the appropriate digital nerves were correlated with subjective reports of paraesthesiae and changes in the compound action potential evoked by constant submaximal stimuli delivered at 1/s from a constant current source. For these experiments (and for those involving digital nerve blocks, *see* fig. 4), the compound sensory potential was recorded using subdermal needle electrodes, as described elsewhere (Applegate and Burke, 1989). Digital nerve blocks were produced in 3 experiments by a tight rubber band around the middle phalanx. The criteria of a complete digital nerve block were (1) anaesthesia of skin distal to the block to tactile and pin-prick stimuli, and (2) loss of the compound sensory action potential transmitted across the block (*see* fig. 4).

RESULTS

Background neural activity

In all 7 multiunit recordings, repetitive stimulation of the appropriate digital nerves at 200 Hz for 10 min was followed by progressive increase in neural activity, best seen in rectified and smoothed records, beginning 10–30 s after the end of the stimulus train (fig. 1). This increasing neural activity corresponded to the first appearance of paraesthesiae and to their subsequent increase in frequency and intensity. The relatively smooth increase in background neural activity was interrupted by transient bursts, generally corresponding to strong paraesthesiae. There was a clear correlation between neural bursts and paraesthesiae, but this was not perfect (*see* fig. 1), presumably reflecting the fact that the neural recordings sample best the activity near the electrode tip, from only one of two stimulated digital nerves.

In 5 of 7 single-unit recordings, spontaneous activity appeared or assumed an irregular bursting pattern following intrafascicular stimulation at 200 Hz for 10 min (figs 2, 3). With the remaining 2 units, the stimulation produced no detectable change in background activity or response to skin stimulation. With these 2 unaffected units, it was possible to discriminate a second afferent potential in the relevant recording. The larger unit in fig. 2A had no background discharge but responded to maintained indentation of the skin at the receptor site. The induced discharge was phase-locked to the test stimuli used to set the stimulus level for the 200 Hz train, as also was the basal discharge of a smaller afferent (indicated by an arrow in fig. 2A). Stimulation at 200 Hz for 10 min altered the discharge of the smaller unit (fig. 2B; *see* below) but failed to affect the response of the larger unit to indentation and did not cause it to become spontaneously active.

The second unaffected afferent innervated a basally active slowly adapting

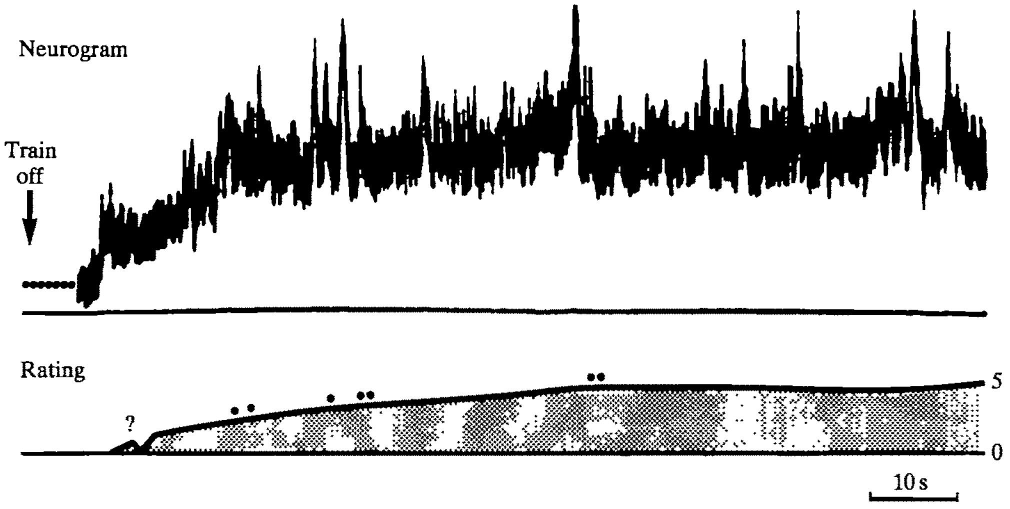

FIG. 1. Poststimulation increase in multiunit neural activity from a fascicle innervating the radial side of the left middle finger. Neural activity has been full-wave rectified and integrated using a RC low-pass filter (time constant 0.5 s). The amplifier was switched on 5 s after the end of the 10 min stimulus train. The dotted line at the beginning of the neural activity represents the level of prestimulation neural activity. The afferent activity began to increase a few seconds later with intermittent bursts of neural activity, occurring in parallel with the subject's reports of paraesthesiae. The initial part of the rating scale for paraesthesiae was redrawn from the strain gauge record and the subsequent part from the subject's verbal reports, the filled dots representing particularly intense paraesthesiae. The first 5 dots were reported verbally and indicated by forceful taps on the strain gauge. The last 2 dots were reported verbally.

receptor. This afferent's background activity and response to skin stimuli were the same after the 10 min stimulus train as before it but, some 30 s after the end of the train, a previously silent afferent began to discharge in irregular spontaneous bursts. The newly active afferent innervated a rapidly adapting receptor, 2 cm proximal to the slowly adapting unit.

The overall discharge of the affected basally active slowly adapting unit in fig. 2 (9 Hz) was not altered by repetitive stimulation. However, instead of a single impulse every 110 ms, it generated a burst of 2 or 3 impulses at an instantaneous frequency of 200 Hz, the burst recurring every 110 ms (fig. 2B). This pattern is consistent with the view that receptor mechanisms were not altered by the stimulation but that each receptor discharge resulted in multiple afferent spikes, the multiplication occurring at some site between receptor and recording site. This view is also consistent with figs 8 and 9 of Ochoa and Torebjörk (1983). Fig. 3 illustrates the findings with 4 of the 5 afferents affected by repetitive stimulation. This slowly adapting unit maintained a steady discharge of 8 Hz before it was stimulated repetitively at a stimulus level greater than that required to phase-lock its discharge to the stimulus (fig. 3A). Following the stimulus train, it remained spontaneously active but discharged intermittently in high-frequency bursts that gradually became briefer and more irregular as they subsided (fig. 3B). Of the 7

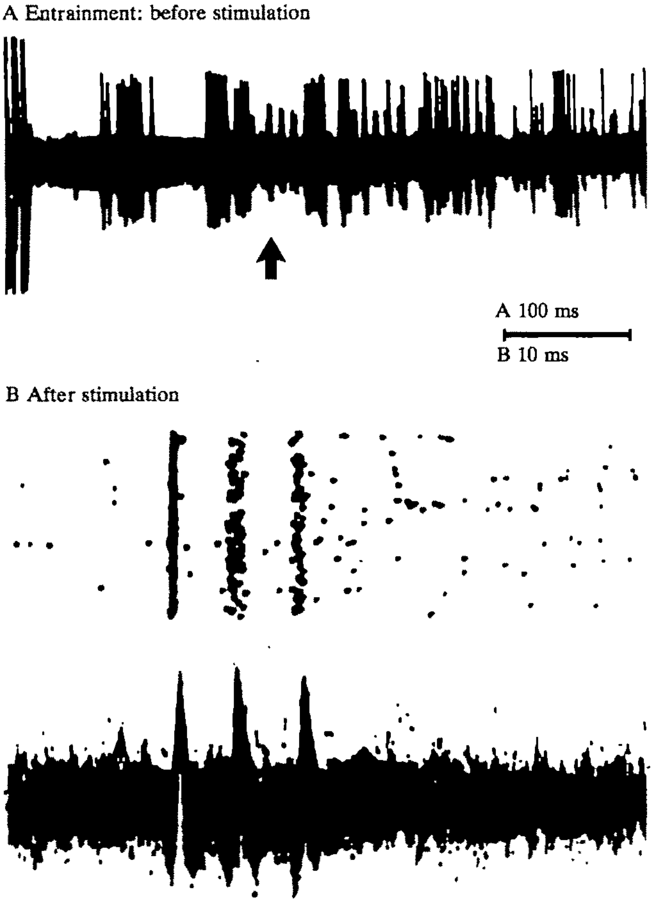

FIG. 2. Poststimulation alteration in the discharge of a slowly adapting afferent unit (the small spikes in A) innervating the radial side of the middle phalanx of the left index finger. A, 12 superimposed sweeps of the original neural activity showing entrainment of the afferent spikes from 2 units by the intrafascicular stimulus, delivered at the beginning of the sweep. The large afferent was induced to discharge by maintained skin indentation. The small afferent was basally active but was silenced for 200 ms by the stimuli, resuming its discharge at the vertical arrow. B, recording obtained 3 min after the end of repetitive stimulation, showing a Z-modulated raster of the discharges of the small afferent. The sweep is triggered intermittently by the first discharge of a burst of 3 impulses and the display is delayed in real time by 14 ms. Note that the afferent discharges 2-3 spikes separated by approximately 5 ms. *Lowest trace*: superimposed sweeps of the original spikes. The larger unit was not affected by the stimulus train and remained silent unless directly stimulated (as it had been for A).

single afferents, both rapidly adapting units were affected by repetitive stimulation, as were 3 of 5 slowly adapting units.

Source of the paraesthesiae

The preceding findings establish that the paraesthesiae induced by repetitive stimulation are associated with spontaneous bursts of activity in the stimulated afferents. They do not establish whether this activity arises from the receptor, the

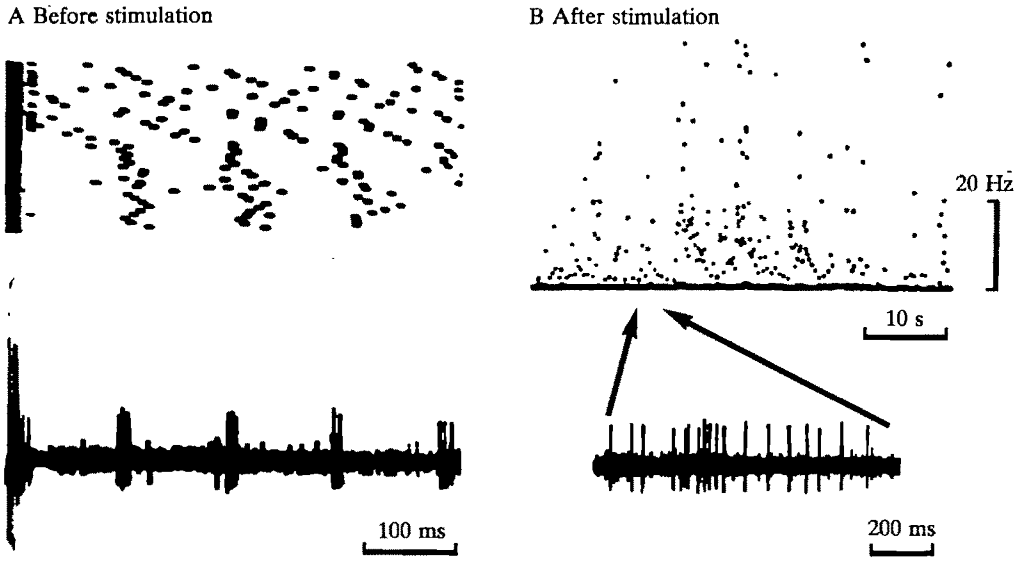

FIG. 3. Poststimulation alteration in the discharge of a slowly adapting afferent unit innervating the ulnar side of the distal phalanx of left middle finger. A, Z-modulated raster display of the afferent spikes in response to an increasing intrafascicular stimulus, delivered at the beginning of the sweep. Initially the stimulus was subthreshold for the afferent and did not entrain its discharge. The last 20 stimuli were above its threshold, reset the afferent's discharge and produced clear entrainment to the stimulus. The lower trace contains superimposed sweeps of original neural activity showing the afferent discharge locked to the stimulus. B, instantaneous frequency plot of the afferent's discharge showing irregularly occurring high-frequency bursts of impulses, 4 min after the end of the stimulus train, shortly before the cessation of spontaneous activity. The inset shows original neural activity on an expanded time-base.

afferent terminals, the afferent nerve trunk or the cell body in the posterior root ganglion, though the discharge pattern in fig. 2B is evidence against the first possibility. In 3 experiments, the digital nerves were stimulated repetitively using ring electrodes around the proximal phalanx after an ischaemic/compression block of the digital nerves had been induced by a tight rubber band around the middle phalanx (fig. 4). When the digit was insensate to tactile and pin-prick stimuli distal to the block and the compound action potential evoked by stimulation through a second set of ring electrodes around the distal phalanx could no longer be recorded (fig. 4B), stimulation at 200 Hz for 10 min was performed proximal to the block (fig. 4D). After the 10 min trains each subject experienced paraesthesiae involving the entire digit, more severe in the insensate distal half, even though the digital nerves were incapable of transmitting across the block (fig. 4E). Removal of the block was then associated with gradual recovery of afferent conduction from distal phalanx to the wrist (fig. 4F). In these experiments not only did the block prevent the repetitive stimulation from affecting distal cutaneous receptors but, even if the abnormal neural discharges had arisen from the afferent terminals or the receptor, they would have been prevented from propagating centrally by the block.

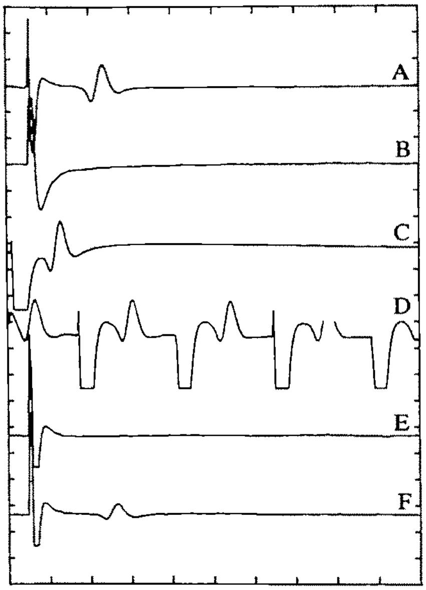

FIG. 4. Effect of digital nerve block on paraesthesiae induced by repetitive stimulation proximal to the block. A, compound sensory action potential recorded by subdermal needle electrodes at the wrist in response to stimulation of the digital nerves of the index finger using ring electrodes around the *distal* phalanx. B, recording as in A but made after an ischaemic block of the digital nerves using a tight rubber band around the middle phalanx, demonstrating that the block was electrically (as well as clinically) complete. C, maximal sensory potential to stimulation proximal to the block using ring electrodes around the *proximal* phalanx. D, sensory potentials recorded at the wrist during repetitive stimulation at 200 Hz for 10 min using ring electrodes around the proximal phalanx. E, response to distal stimulation to confirm that the block was still complete when the subject was experiencing paraesthesiae in the insensate half of the finger 2 min after the train. F, sensory potentials to distal stimulation after release of the block showing a small potential at long latency, indicating as yet incomplete recovery. A, B, C, E and F are averages of 256 responses. D is a single sweep, not stimulus-locked. A, before ischaemia; B, C, during ischaemia; D, train at 200 Hz; E, after train; F, ischaemia released. Vertical calibration scale = 5 μV intervals, horizontal scale = 2 ms intervals.

Electrically evoked neural activity

With multiunit neural recordings electrical stimuli of constant current were applied to the digital nerves after the paraesthesiae had begun to subside (some 3–7 min after the end of repetitive stimulation), in order to define the prolonged postactivation depression of axonal excitability and compare it with the ability of the axons to transmit naturally evoked activity (*see* next section). Inevitably, the timing of these stimuli was not optimal for demonstrating the transient postactivation increase in axonal excitability (Applegate and Burke, 1989; *see* fig. 8). Nevertheless, in 3 studies out of 7, the compound sensory action potential was larger in amplitude and area by 2.8–9.3% than before the stimulus train. The radiating sensation induced by these test stimuli was maximal in the pulp of the digit, indicating that this site was the major source of the afferents contributing to the compound sensory action potential.

Following repetitive stimulation, the latencies of the individual components of the compound sensory action potential increased by 0.07–0.29 ms (i.e., 3.6–10.5% of the control values) and the degree of dispersion increased by up to 15% (fig. 5). These changes were usually greatest in the first recordings obtained after the end of the repetitive stimulation (at 3–7 min) and then became progressively less. They occurred with the maximal sensory action potential (fig. 5B) as well as submaximal afferent volleys (fig. 5A).

In all recordings, the amplitude of the afferent volley evoked by a constant submaximal stimulus current then became progressively smaller with increasing time after the end of stimulus train, reaching a nadir 20–30 min after the end of the train (figs 5A, 6A, 7A, 8), at which time the subjects commonly experienced

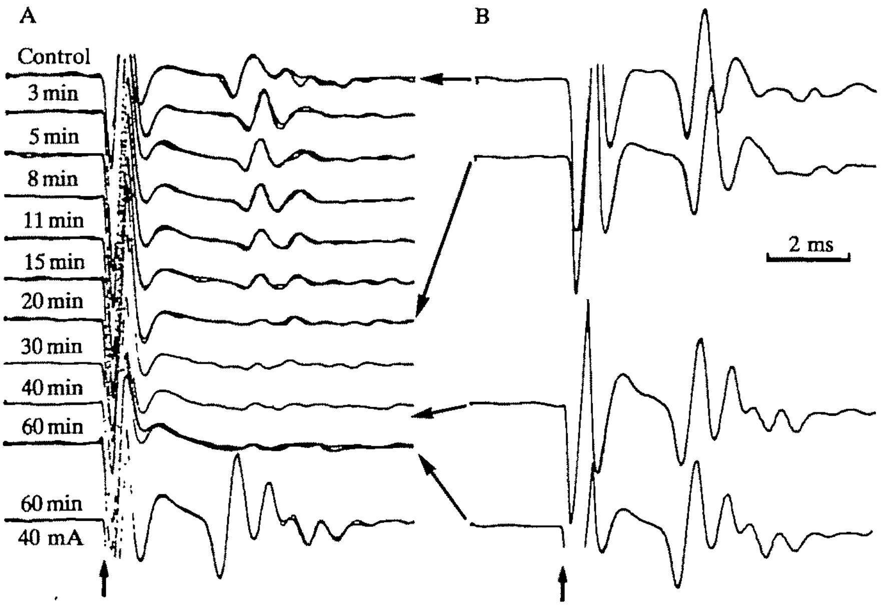

FIG. 5. Effects of a 10 min stimulus train on submaximal (A) and maximal (B) compound sensory action potentials, evoked using stimuli of 20 mA and 40 mA, respectively. The nerve fascicle innervated the radial side of the right ring finger. The initial traces represent the pretrain recordings; the subsequent traces were obtained at the times indicated after the end of the stimulus train. Note that in A the greatest increase in latency occurred in the initial posttetanic recording, when there was as yet no suppression of the compound sensory potential. At 20–60 min the response to the submaximal stimulus was profoundly depressed but a maximal potential could be obtained using the stronger stimulus. Each trace contains the average of 16 responses and, in A, 1, 2 or 3 consecutive averages are superimposed to demonstrate reproducibility. As in subsequent figures the stimuli were delivered at the vertical arrow.

difficulty in detecting the stimuli. Often it became impossible to restore the test potential to its control size despite a five-fold increase in stimulus current (fig. 7A). Similarly the available current (100 mA) sometimes proved insufficient to evoke a maximal compound sensory action potential, whereas 30–40 mA had been adequate before the train (fig. 7A). These data provide direct confirmation of findings of Applegate and Burke (1989) using a different recording technique.

Mechanically evoked neural activity

The response to natural stimuli applied to the pulp of the appropriate terminal phalanx was not altered by repetitive stimulation at 200 Hz for 10 min. Even when the depression of the amplitude of submaximal test potentials evoked by electrical stimuli was greatest (some 20–30 min after the end of the stimulus train), mechanical stimuli evoked a response little different from the control (figs 6B, 7B). In the initial 3 recordings the response to a natural stimulus was assessed qualitatively using maintained indentation or scraping of the skin performed manually. In the subsequent 4 recordings a reproducible skin stimulus was delivered by the vibrator and the evoked neural activity was rectified, smoothed

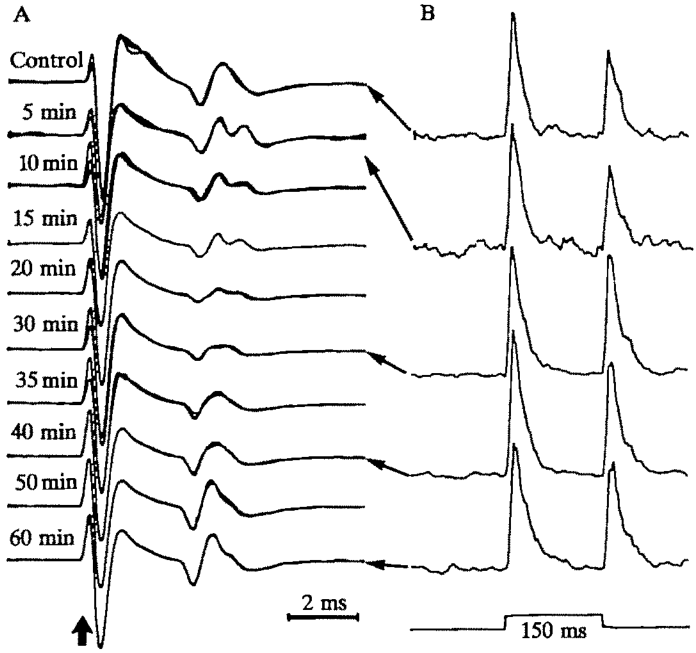

FIG. 6. Effects of a 10 min stimulus train on electrically evoked (A) and mechanically evoked (B) compound sensory action potentials from a fascicle innervating the ulnar side of the right middle finger. The stimulus current for all traces in A was 20 mA, and each trace shows 3 consecutive averages, each of 4 responses. For B, 16 sweeps were averaged after the neurogram was rectified and smoothed using an RC low-pass filter (time constant 0.01 s). The mechanically induced potentials consist of large 'on' and 'off' responses with little maintained activity during the steady indentation. The pulse driving the vibrator is shown as the bottom trace in B. In both A and B, the pretrain responses are shown in the upper traces and the posttrain responses were obtained at the indicated times.

and averaged (figs 6B, 7B). In these recordings there were small changes in the 'on' and 'off' responses in the different averaging runs in any one experiment. However, the changes occurred in either direction, and there was no trend for the poststimulation responses to become bigger or smaller with elapsed time ($P > 0.5$ for each experiment). The poststimulation 'on' and 'off' responses were therefore averaged and compared with the corresponding control 'on' and 'off' responses. In none of the individual recordings was the prestimulation control response outside 2 SDs of the mean poststimulation response. Considering the poststimulation recordings together, the mean 'on' and 'off' responses were 99.8% and 114% of their controls, neither representing a statistically significant change.

It can be concluded that the depression of axonal excitability to electrical stimulation does not prevent axonal activation by natural stimulation through the receptor.

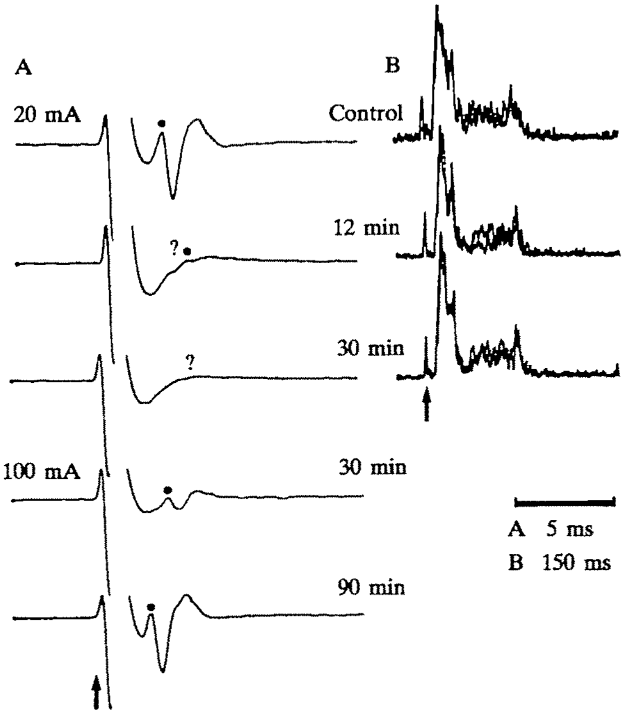

FIG. 7. Effects of a 10 min stimulus train on electrically (A) and mechanically (B) evoked compound sensory action potentials from a fascicle innervating the radial side of the left index finger. Similar format as for fig. 6. The traces in A are single averages of 16 responses. In A the first 3 traces (pretrain; 12 min posttrain; 30 min posttrain) were obtained using a submaximal stimulus of 20 mA. For the fourth and fifth traces, the stimulus current was increased to 100 mA but only with the fifth trace, 90 min posttrain, did the electrically evoked volley reach the control size. The round dot on each trace indicates the initial negative peak of evoked compound action potential when it could be identified. The traces in B contain 2 consecutive averages each of 16 responses, in which the neural activity has been full-wave rectified, but not smoothed as in fig. 6 in order to demonstrate the maintained afferent discharge during the steady indentation, in addition to the prominent 'on' and smaller 'off' responses. The small deflexion at the arrow is artefact due to the driving pulse to the vibrator.

Perceptual disturbances

The ability to detect cutaneous stimuli was quantified using calibrated von Frey hairs before and after repetitive stimulation of the digital nerves of the index finger at 200 Hz for 10 min. Within 1-2 min of the cessation of the stimulus train, axonal excitability was increased, such that, in the 3 subjects, the amplitude of the test volleys reached 118%, 148% and 142% of the pretrain control. At this time, each subject experienced paraesthesiae and the thresholds for perception of punctate stimuli increased dramatically (from < 0.3 g to 6.9 g, from 4.1 g to 14.8 g and from 6.9 g to 36 g, respectively). In each subject, the time course of the paraesthesiae corresponded to that of the increase in axonal excitability, the paraesthesiae subsiding as the excitability began to decline (fig. 8). In subjects 1 and 2 the perceptual threshold remained elevated above the pretrain values when the paraesthesiae subsided (fig. 8). In subject 1, the threshold remained elevated for

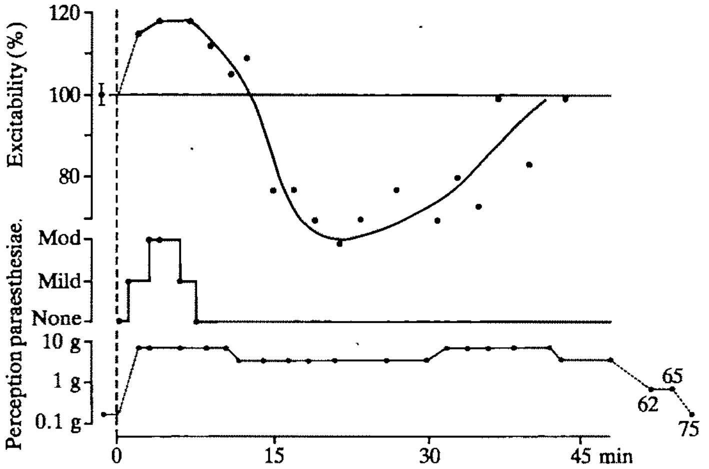

FIG. 8. Perceptual consequences of a 10 min stimulus train. The posttrain changes in axonal excitability (*upper trace*) are expressed as a percentage of the pretrain value. The amplitude of the pretrain test potential was 31% of maximum. Each data point is the average of 16 responses. Paraesthesiae (*middle trace*) were graded subjectively as absent, mild, moderate or strong. Tactile sensibility (*lowest trace*) was measured as the ability to detect punctate stimuli delivered using von Frey hairs, perceptual threshold defined as the detection of 8 of 10 stimulus presentations. Note that perceptual threshold did not return to control values until 75 min after the train. The vertical line at time 0 represents the end of the train. The data points to left of this line represent pretrain control data (*upper trace*: mean amplitude of the test potential, with the range of 3 determinations given by the error bars; *lowest trace*: threshold for detection of tactile stimuli, < 0.3 g).

> 65 min, and in subject 2 it decreased as the paraesthesiae subsided but remained elevated at 6.9 g, above the control level (4.1 g) until the experiment was terminated 30 min after the stimulus train. In the third subject, the threshold returned to the control level as the paraesthesiae subsided even though axonal excitability decreased to a trough of 54% at 22 min, before recovering slowly to 100% at 47 min.

These experiments establish that perceptual threshold is maximally elevated during the paraesthesiae, when axonal excitability is elevated, and that it *may* remain elevated for long after the subsidence of paraesthesiae. There is no correlation between axonal excitability as tested using electrical stimuli and the ability to detect discrete tactile stimuli applied to the skin.

DISCUSSION

Prolonged high-frequency stimulation of cutaneous sensory axons is followed by a transient increase in excitability lasting a few minutes superimposed on a profound hypoexcitability that is maximal at 20–30 min but may last over 1 h (Applegate and Burke, 1989). The present findings suggest that the transient hyperexcitability is associated with a bizarre discharge from some axons, consisting of ectopic impulses and high-frequency repetitive bursts of impulses. As discussed below, this disordered pattern of axonal activity probably accounts for the subjective paraesthesiae. On the other hand the long-lasting depression of axonal excitability may well be of little clinical consequence because the very axons that are hypoexcitable electrically can be activated quite readily and apparently normally through their receptors. It is likely then that the positive symptoms produced by repetitive activation of cutaneous afferents arise peripherally, in the disturbed afferents, but that the negative symptoms do not.

Poststimulation paraesthesiae

The evidence that peripheral mechanisms suffice to explain paraesthesiae is now quite strong (for a thorough review, *see* Culp and Ochoa, 1982). Using intrafascicular microstimulation of single cutaneous afferents, Ochoa and Torebjörk (1983) and Vallbo *et al.* (1984) have argued independently and together (Torebjörk *et al.* 1987), that impulses in single afferents may be perceived and are referred to discrete punctate skin regions that correspond closely if not exactly to the innervation zones of the afferents. Paraesthesiae can be viewed as impulse trains set up spontaneously rather than by natural stimulation of the receptor (*see* Culp and Ochoa, 1982). In the present postactivation model, the time course of paraesthesiae parallels the time course of axonal hyperexcitability and is associated with disturbed spontaneous firing of cutaneous afferents.

From the results illustrated in figs 2 and 4, this disturbed firing probably arises from a disorder of the axon or of the cell body rather than a disorder at receptor level. It is possible that there is more than one focus of ectopic activity in any one axon reflecting focal enhancements of axonal excitability. Certainly the increase in excitability probably occurs throughout the axon (Applegate and Burke, 1989) with local factors determining the sites of greatest excitability. However, this is clearly not the case with other forms of paraesthesiae such as those induced by a compressive injury (Ochoa and Torebjörk, 1980), Lhermitte's phenomenon, sciatica and peripheral nerve injury (Nyström and Hagbarth, 1981; Nordin *et al.*, 1984). The common factor in all these cases remains that positive symptoms such as paraesthesiae can be adequately explained by ectopic impulse generation in disturbed cutaneous afferent fibres.

It is unlikely that all large myelinated cutaneous afferents activated by the prolonged stimulus train contribute to postactivation paraesthesiae. There are two reasons for this view. First, of the four types of cutaneous mechanoreceptor in glabrous skin, the slowly adapting type II unit appears not to evoke a sensory percept when stimulated in isolation (Ochoa and Torebjörk, 1983; Vallbo *et al.*, 1984), and would presumably not produce paraesthesiae even if it developed the appropriate discharge pattern. Secondly, postactivation paraesthesiae are felt as fleeting discrete punctate sensations, suggesting that only some axons are spontaneously active at any one time. If all were active, the subject would presumably experience a fused coalescent sensation involving the whole digit, much as during the stimulus train itself.

In previous studies it was found that only afferents of low electrical threshold developed hyperexcitability after repetitive stimulation for 10 min (Applegate and Burke, 1989) but the explanation for this was unclear. It could have been due to the more secure driving of low-threshold afferents by the stimulus train. However, if all adequately stimulated afferents do undergo qualitatively similar excitability changes, it is probable that these changes will differ quantitatively for different axons and possibly also for different sites in the one axon. For example, it is possible that the phenomenon responsible for the hyperexcitability is the passive accumulation of extracellular potassium (Schoepfle and Katholi, 1973; Raymond, 1979; Barrett and Barrett, 1982; Kocsis *et al.*, 1983; Bostock and Grafe, 1985; Low, 1985), and there will inevitably be local variations in potassium concentration throughout any one nerve fascicle. Indeed high potassium concentrations could produce conduction block in some axons (Orchardson, 1978; Kocsis *et al.*, 1983; Lisney and Devor, 1987). In the present study, 2 afferents of 7 that could be effectively stimulated did not develop a disturbed discharge pattern after the stimulus train.

Poststimulation hypaesthesia

One of the most impressive findings of the present study was the preservation of the mechanically evoked afferent volley when the electrically elicited volley was grossly attenuated or even abolished. At least with normal nerves and normal cutaneous receptors, the depression of axonal excitability produced by repetitive stimulation constitutes a minor barrier to the transmission of impulses set up by natural stimuli.

This finding might have been anticipated. Prolonged high-frequency vibration of muscle using stimulus parameters selective for group Ia afferents has been used in both cat and man to raise the threshold of Ia afferents to subsequent electrical stimuli such that a pure group Ib volley could be evoked (Coppin *et al.*, 1970; Fetz *et al.*, 1979; Jankowska and McCrea, 1983; Heckman *et al.*, 1984). During the postvibratory depression of Ia excitability to electrical stimulation, mechanical stimuli still elicit normal Ia responses (Jankowska and McCrea, 1983) and, according to Heckman *et al.* (1984), the tendon jerk is enhanced rather than depressed. Similarly, secure driving of pacinian corpuscles by vibration at 300 Hz for 10 min produces minimal depression of their response to subsequent test stimuli, any depression being transient, lasting only a couple of minutes (O'Mara *et al.*, 1988).

A further implication of the present findings is that, with initially normal receptors and cutaneous afferents, the poststimulation depression of cutaneous sensibility as tested using external stimuli is probably due to a central phenomenon, rather than the depression of peripheral axonal excitability. This conclusion has experimental precedents. For example, in human subjects, prolonged cutaneous vibration results in diminished vibrotactile perceptual acuity (*see*, e.g., Wedell and Cummings, 1938; Gescheider and Wright, 1969; Gescheider *et al.*, 1979). Such stimulation depresses the responsiveness of relay neurons in the cuneate nucleus to a much greater degree and for a much longer period than is seen with the primary afferent fibres (O'Mara *et al.*, 1988). There are also striking parallels with the studies of Nathan (1958), who studied the paraesthesiae and hypaesthesia occurring at different stages during and following a period of nerve ischaemia. In the immediate postischaemic period, when subjects experienced paraesthesiae, they failed to detect peripheral stimuli even though an adequate afferent volley entered the central nervous system. These experiments indicated that the 'masking' of the test stimulus occurred centrally, at synaptic relays 'bombarded by a profusion of impulses arriving from the nerve which is discharging spontaneously' (Nathan, 1958, p. 19). In the present experiments with prolonged high-frequency repetitive stimulation of cutaneous afferents, the elevation of perceptual threshold was maximal during the poststimulation paraesthesiae in all 3 subjects and persisted long after the subsidence of paraesthesiae in 2 of the 3 subjects (*see* fig. 8). The spontaneous activity responsible for paraesthesiae presumably contributes to decreased tactile acuity (Gilliatt and Wilson, 1954) but would do so only for the duration of the spontaneous activity. When the hypaesthesia outlasts the paraesthesiae, as in fig. 8, it seems prudent to invoke an additional mechanism, such as a long-lasting functional abnormality at synaptic relays that have been subjected to an unusually intense and prolonged afferent barrage during the 10 min stimulus train (*see* O'Mara *et al.*, 1988).

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LOCAL BRAIN HAEMODYNAMICS AND OXYGEN METABOLISM IN CEREBROVASCULAR DISEASE

POSITRON EMISSION TOMOGRAPHY

by G. SETTE, J. C. BARON, B. MAZOYER, M. LEVASSEUR,
S. PAPPATA *and* C. CROUZEL

(*From the Service Hospitalier Frédéric Joliot, Commissariat à l'Energie Atomique, Département de Biologie, Orsay, France*)

SUMMARY

Using positron emission tomography (PET) and equilibrium imaging with oxygen-15 labelled gases, the cerebral blood flow (CBF), blood volume (CBV), oxygen extraction fraction (OEF) and oxygen consumption rate ($CMRO_2$) were measured in multiple regions of interest over the cerebral cortex of 5 control subjects, 4 patients with strictly unilateral longstanding carotid artery occlusion, 1 patient with middle cerebral artery embolic stroke in the acute stage, and 4 patients with subcortical stroke and no cervical arterial disease. In each control subject, the regional CBV was linearly and positively correlated with both CBF and $CMRO_2$, while the local mean transit time ($t = CBV/CBF$) was uniformly distributed, reflecting the local adaptation of both the vascular tone and the capillary density to the metabolic demand at constant cerebral perfusion pressure that characterizes the normal brain. In patients with subcortical stroke, cortical blood volume was reduced in proportion to the matched reduction in CBF and $CMRO_2$, suggesting that the metabolic depression resulting from cortical deafferentation increases the resting tone of pial vessels. Unilateral carotid occlusion induced larger CBV and t, and steeper slopes of the CBV-CBF relationship, particularly on the occluded but also on the patent side. The assessment of the local cerebral perfusion pressure (CPP) as judged by the ratio CBF/CBV in 3 patients with focally raised OEF and preserved or reduced $CMRO_2$, allowed the demonstration in multiple cerebral regions of single patients of two well-known physiological phenomena: the autoregulation of CBF, followed by the rise of the OEF as local CPP falls further. In addition, the depression of $CMRO_2$ in the ischaemic cortex was associated with a trend for CBV to return towards normal values, compared with the maximally elevated CBV found in oligaemic but metabolically normal areas. This suggests that a process of metabolic vasoconstriction may participate, among other factors, in the vascular collapse that occurs, and would serve to regenerate some haemodynamic reserve, at very low CPP levels.

INTRODUCTION

The use of positron emission tomography (PET) in cerebrovascular disorders has greatly improved our understanding of the clinical pathophysiology of cerebral

Correspondence to: Dr J. C. Baron, Service Hospitalier Frédéric Joliot, CEA, Département de Biologie, 91406 Orsay, France.

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ischaemia, both in the acute and the chronic state (Ackerman *et al.*, 1985; Baron, 1985; Frackowiak, 1985; Powers *et al.*, 1985*b*); particularly, the measurement of regional cerebral blood flow (CBF), oxygen consumption ($CMRO_2$), oxygen extraction (OEF) and, more recently, blood volume (CBV) has permitted the identification of three successive stages of severity which are characterized respectively by (1) an isolated rise of CBV (reflecting a vasodilatation that largely underlies the mechanism of CBF autoregulation); (2) a moderate fall in CBF with normal $CMRO_2$ and increased OEF (a fully compensated stage defining oligaemia); and (3) a depression of $CMRO_2$ as CBF falls further (defining true ischaemia). While stage 1 involves only the haemodynamic reserve, in stages 2 and 3 the reserve of oxygen extraction is also called upon (the 'misery perfusion syndrome', Baron *et al.*, 1981). In addition to cerebral ischaemia per se, PET studies have also helped to establish the phenomena that take place after infarction, during reperfusion (both characterized by a low OEF), and in brain areas distant from the site of actual damage (Baron, 1985; Feeney and Baron, 1986).

Despite these advances, the full potential of PET to investigate these variables in individual brain regions of single patients has been exploited only rarely (Lenzi *et al.*, 1982; Baron *et al.*, 1984; Kanno *et al.*, 1988). Yet this may provide a more accurate and more complete understanding of the phenomena in play. Hence in most key reports, the analysis of the data implied either 'whole brain' or 'whole cortex' in individual patients (Wise *et al.*, 1983; Gibbs *et al.*, 1984; Powers *et al.*, 1984, 1985*a*, 1987) or small regions in groups of patients (Leblanc *et al.*, 1987).

In the present work, we report a detailed analysis of the local interrelationships of CBF, CBV, OEF and $CMRO_2$ in cortical areas of selected individual patients spanning the whole spectrum of cerebral haemodynamic failure. In addition to extending our knowledge on cerebrovascular pathophysiology, the results also reveal a new facet of the application of PET in this field.

PATIENTS AND CONTROL SUBJECTS

We have studied 5 control subjects free of cerebrovascular risk factors, and 9 patients with cerebrovascular disease (Table 1). These 9 were selected on the following basis. (1) Group I: predominantly subcortical stroke without significant cervical artery disease, in whom the PET scan disclosed cortical areas with statistically significant 'pure metabolic depression' (PMD, a decrease in $CMRO_2$ without alteration in the OEF). (2) Group II: unilateral carotid artery occlusion without haemodynamically significant contralateral carotid disease. From our files, we extracted 8 patients fulfilling these criteria, 4 in each group (group I, patients 1–4; group II, patients 5–8) (*see* Table 1 for details).

In addition, we have included in our analysis one patient (Case 9) with acute ischaemic stroke in the carotid territory, not directly belonging to any of the two above groups, but of special interest as his PET study was performed while severe focal ischaemia was still present.

METHODS

Tomographic images of CBF, $CMRO_2$, OEF and CBV were obtained by means of the ^{15}O continuous inhalation method, using successive inhalation of tracer amounts of $C^{15}O_2$, $^{15}O_2$ and

$C^{15}O$ (Jones *et al.*, 1976; Subramanyam *et al.*, 1978; Frackowiak *et al.*, 1980; Lebrun-Grandié *et al.*, 1983; Pantano *et al.*, 1985), and the 4-ring LETI-TTVO1 time of flight positron camera (slice thickness and lateral resolution of 12 mm for the direct planes) which permits the simultaneous collection of 7 slices (4 direct and 3 cross-planes, with an undetected interslice space of about 3 mm) (Soussaline *et al.*, 1984).

The subject was comfortably positioned in a head-holder so that the lowest slice was located 10 mm above and parallel to the orbitomeatal line, by means of a crossed laser beam system. A ^{68}Ge–^{68}Ga transmission scan was performed before gas inhalation, for attenuation correction.

The $C^{15}O$ gas was produced in a continuous flow (Pantano *et al.*, 1985). A mixture of 0.25% O_2 in N_2 was used as the combined target and sweep gas, the target pressure being 2 atmospheres above atmospheric pressure. Bombardment was performed using a 20-μA/8-MeV deuteron beam degraded to 6.5 MeV by the entrance foil of the target. The product of the $^{14}N(d,n)\,^{15}O$ reaction was $^{15}O_2$; this was then converted to $C^{15}O$ by activated charcoal at 900° C, which also removed the impurities. After furnacing, the traces of $C^{15}O_2$ produced by the reaction (about 5%) were removed by a soda line trap.

The gas was piped to the positron tomograph at a CO concentration of 0.4%, a flow rate of 500 ml/min (maximal concentration of stable CO inhaled, 0.03%) and a specific activity of 0.03 mCi/ml. Production of the $C^{15}O_2$ and $^{15}O_2$ gases has been detailed elsewhere (Baron *et al.*, 1978).

During each of the 3 successive ^{15}O scans, blood samples were withdrawn in duplicate from a radial artery catheter, to measure the ^{15}O radioactive concentration in whole blood and plasma as well as the PaO_2, $PaCO_2$ and pH; the haematocrit and haemoglobin values were also obtained.

The PET images were transformed pixel by pixel into quantitative CBF ($ml \cdot 100\ ml^{-1} \cdot min^{-1}$), OEF (dimensionless), $CMRO_2$ ($ml \cdot 100\ ml^{-1} \cdot min^{-1}$) and CBV ($ml \cdot 100\ ml^{-1}$) images using the ^{15}O blood data and the equations described by Jones *et al.* (1976) and Frackowiak *et al.* (1980), taking into account the nonextracted intravascular labelled oxyhaemoglobin (Lammertsma *et al.*, 1983). For this correction of the OEF, the $C^{15}O$ steady-state method was used, according to previously published methods (Lammertsma *et al.*, 1983; Pantano *et al.*, 1985), which permits the direct correction of the $^{15}O_2$ scan without having to generate images of the uncorrected OEF, the CBV or the CBF, and which is independent of the regional cerebral haematocrit (Lammertsma *et al.*, 1987). To generate the regional CBV image (in $ml \cdot 100\ ml^{-1}$), the $C^{15}O$ steady state image was transformed pixel by pixel according to the following equation (Lammertsma *et al.*, 1987):

$$\mathrm{rCBV} = \frac{100}{\rho\left(\dfrac{\mathrm{Ca}}{\mathrm{Ct}} - \dfrac{\lambda}{\mathrm{CBF}}\right)} \qquad (1)$$

where Ca and Ct are the whole blood and the pixel ^{15}O concentrations during $C^{15}O$ equilibrium imaging, respectively, λ is the ^{15}O decay constant ($0.334 \cdot min^{-1}$), and ρ is the ratio of cerebral-to-peripheral haematocrit, taken here as a constant value of 0.85 (Martin *et al.*, 1987); the CBF value is the corresponding pixel CBF value obtained from the $C^{15}O_2$ scan as described above. With respect to Ca, it must be emphasized that, in the $C^{15}O$ method, blood radioactivity must be exclusively present in erythrocytes and practically undetectable in plasma (Martin *et al.*, 1987); this was checked in each patient reported here.

DATA PROCESSING

A standardized method for regional data analysis using circular regions of interest (ROIs) ($3\ cm^2$) was employed. This method, developed in our laboratory, has been described in detail elsewhere (Laplane *et al.*, 1989). Briefly the ROIs are positioned on the CBF image along the cortical rim of one cerebral hemisphere, tangentially to each other as well as to an outer computer-generated isocontour set at 30% of maximal pixel CBF; these ROIs are then mirror-copied on the opposite hemisphere, with respect to an anteroposterior axis itself located visually so that the mirror isocontour closely superimposes on the original one; in this method, subjective judgement is reduced to a minimum. This procedure was used both in controls and in patients, except that in the latter, the original set of ROIs was positioned systematically on the unaffected side. Once defined on each CBF image, the whole set of ROIs was translated on the corresponding $CMRO_2$, OEF and CBV images.

The subsequent data analysis was performed on the ROI values, after exclusion of two groups of ROIs: (1) in all studies, those overlying the large cerebral vascular pools, particularly in the vicinity of the dural sinuses and in the sylvian fissure: to this end, all original ROIs (and the homologous contralateral ROI) with rCBV above $8\ \mathrm{ml} \cdot 100\ \mathrm{ml}^{-1}$ were systematically excluded; (2) in the cerebrovascular patients, the ROIs overlying the infarcted areas (defined on corresponding CT and/or MRI scans) were also rejected, together with their contralateral homologous ROIs.

In addition to obtaining the CBF, $CMRO_2$, OEF and CBV values found in each ROI, an asymmetry index was calculated for each pair of homologous ROIs by the ratios right side/left side in controls, and affected side/unaffected side in patients. Using the data from the 5 controls, 95% confidence limits for individual ROIs asymmetry were calculated to allow assessment of asymmetry for either of the measured physiological variables in each patient studied. Finally, the ratios CBV/CBF (corresponding to the cerebrovascular mean transit time t (Grubb *et al.*, 1973) and CBF/CBV (the inverse of t, an apparently reliable index of cerebral perfusion pressure, Gibbs *et al.*, 1984) were also calculated for each ROI selected for analysis. In what follows, the regional value of the measured variable will be denoted by the prefix r (e.g., rCBF, rt).

RESULTS

Physiological variables (*Table 1*)

There were no systematic differences in any of the measured variables among controls, or group I or II patients although, as expected, the mean arterial blood pressure tended to be higher in cerebrovascular disease patients than in controls.

Control subjects

In each control, the rCBV was significantly correlated with rCBF in a positive linear form ($CBV = aCBF + b$). The variability in the slopes found was small (Table 2, fig. 1A), and each of the 5 slopes, except subject 2, was not statistically different from one another (epsilon test). Similar findings were obtained in the analysis of the rCBV-$rCMRO_2$ relationships.

Although a significant linear correlation between rt and rCBF was found in 2 of the 5 control subjects (fig. 1B), in all the slope of this relationship was close to zero. Hence the rt values were fairly constant across the whole range of rCBF in each control, with little intersubject variability in mean t values, suggesting a normal and uniform cerebral perfusion pressure.

Pure metabolic depression (*group I patients*)

From the total set of ROIs defined in the 4 patients of group I, the ROIs with a significant depression of $rCMRO_2$ (affected/unaffected $CMRO_2$ ratio beyond the 95% confidence limits calculated in our group of control subjects) but *without* a

TABLE 1. CLINICAL AND LABORATORY DATA

Control subjects	*Age (yrs)*	*Sex*	*$PaCO_2$ (mmHg)*	*Haematocrit*	*Haemoglobin (mmol/l)*	*pH*	*MABP (mmHg)*
1	54	M	43.8	0.43	9.6	7.39	96
2	33	M	37.3	0.44	9.4	7.40	83
3	32	F	39.7	0.40	8.6	7.40	90
4	40	M	39.8	0.44	9.2	7.37	86
5	30	M	41.6	0.38	9.4	7.36	92

Patients (Case no.)	*Age (yrs)*	*Sex*	*$PaCO_2$ (mmHg)*	*Haematocrit*	*Haemoglobin (mmol/l)*	*pH*	*MABP (mmHg)*	*Clinical features*	*Stroke to PET scan delay*	*Cerebrovascular diagnosis*
1	62	M	39.1	0.39	8.2	7.40	105	R hemiparesis and aphasia	3 mos	Subcortical frontal + insular ischaemic stroke (CT + MRI), unknown aetiology
2	78	F	38.4	0.37	7.8	7.40	90	L sensorimotor deficit and neglect	10 days	R thalamocapsular haemorrhage (CT + MRI)
3	51	F	38.8	0.33	6.9	7.37	86	L sensorimotor deficit	2 mos	R medial thalamic infarct (CT + MRI)
4	57	M	36.2	0.47	9.9	7.41	106	L central facial paresis + motor neglect	20 days	R lenticulocapsular ischaemic stroke (CT + MRI), unknown aetiology
5	69	F	41	0.37	7.5	7.4	93	Multiple R hemisphere TIAs		R ICA occlusion; mild stenosis of left ICA; normal CT scan
6	55	M	35.3	0.51	11.1	7.39	106	Multiple episodes of L amaurosis fugax + R hemispheric RIA		Occlusion of the R common carotid artery. Old vertebro-basilar territory infarct (CT scan)
7	54	M	43.5	0.41	8.9	7.3	93	Multiple episodes of L amaurosis + L hemisphere TIA and minor stroke (R hemiparesis)	1 mo	L ICA occlusion due to arterial dissection; occluded left vertebral artery. Small L frontal corticosubcortical infarct (CT scan)
8	69	F	37.8	0.40	8.5	7.3	133	Multiple episodes of orthostatic ischaemic attacks; minor stroke after carotid angiogram	4 mos 20 days	R preocclusive ICA stenosis, occluded after angiogram. Nonstenotic plaque at origin of L ICA. Corticosubcortical R frontal infarct on CT scan
9	76	M	32.2	0.38	8.2	7.50	106	R hemiparesis and aphasia	1.5 days	Ischaemic stroke with almost complete recovery, due to cardiac embolism

TIA = transient ischaemic attack; RIA = reversible ischaemic attack; ICA = internal carotid artery; MABP = mean arterial blood pressure.

TABLE 2. LINEAR REGRESSION OF rCBV ON rCBF IN CONTROL SUBJECTS

Subject	*Slope+SD*	*Intercept* (*ml·100 ml*$^{-1}$)	*n*	*r*	*P*
1	0.063±0.021	+0.94	36	0.45	<0.01
2	0.107±0.021	−0.46	32	0.69	<0.01
3	0.070±0.006	+0.04	36	0.89	<0.01
4	0.073±0.014	−0.81	48	0.61	<0.01
5	0.073±0.012	+0.90	36	0.70	<0.01

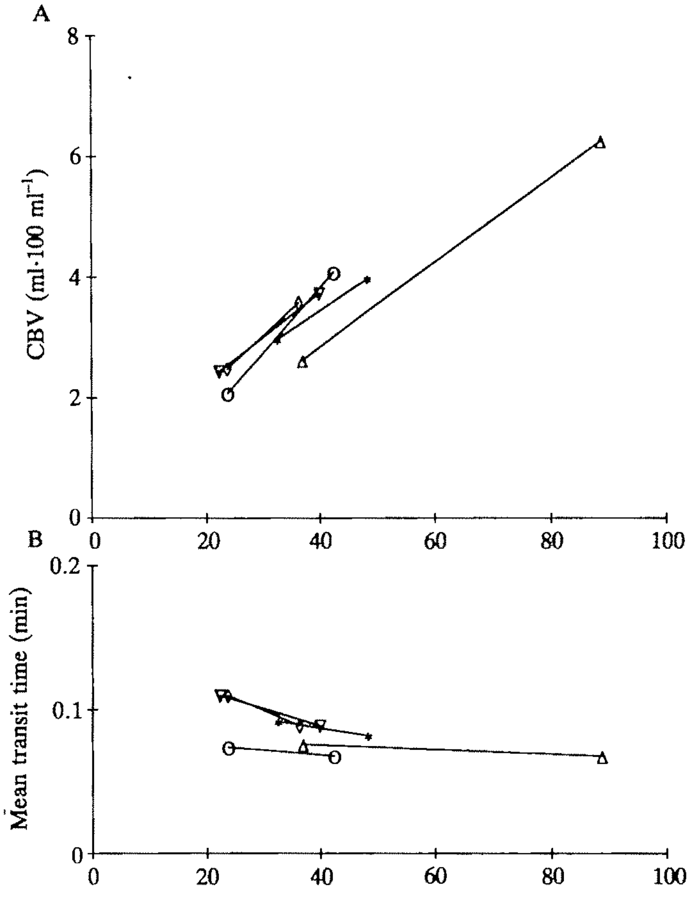

FIG. 1. Relationship between rCBV and rCBF (A) and between rt and rCBF (B) in the grey matter regions of 5 control subjects. For easier identification, only the lowest and highest rCBF values for each control are shown. Each of the rCBV-rCBF linear correlations was statistically significant (*see* Table 2), while the rt-rCBF relationship was significant in 2 controls only (subjects 4 and 5, the linear regressions being $rt = 0.0009\ (\pm 0.0004) \cdot rCBF + 0.13$ and $rt = 0.001\ (\pm 0.0004) \cdot rCBF + 0.14$, $P < 0.05$). * = control 1, circle = control 2, triangle = control 3, inverted triangle = control 4, diamond = control 5.

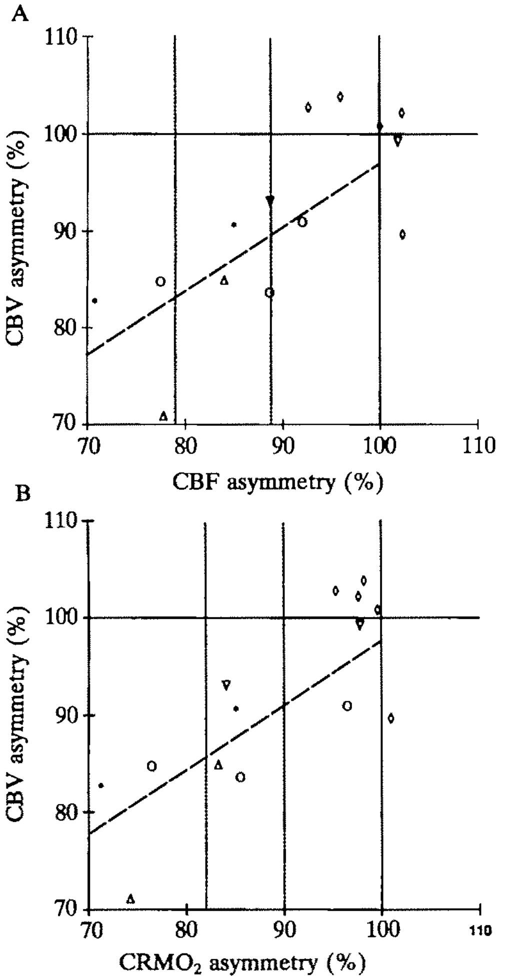

FIG. 2. Percentage CBV asymmetry (affected side/unaffected side) versus corresponding CBF (A) and CMRO$_2$ (B) asymmetries in grey matter areas of 4 patients with subcortical stroke and mild to significant degrees of cortical pure metabolic depression (i.e., essentially matched decrease in rCBF and rCMRO$_2$). The original ROIs in each patient were grouped according to the degree of CMRO$_2$ asymmetry, assessed relative to normal confidence limits as within 1 SD, between 1 and 2 SDs, and >2 SDs from controls (the SDs are shown as dotted lines). For comparison, the values found in 5 normal subjects are also shown. There was a proportional fall in rCBV as rCBF and rCMRO$_2$ decreased in metabolic depression, depicted here by the significant regression lines found: rCBV% = 0.66 ($\pm$0.21)·rCBF%+31.1, n = 9, $P<0.02$ and rCBV% = 0.67 ($\pm$0.21)·rCMRO$_2$%+30.7, n = 9, $P<0.02$. * = Case 1, circle = Case 2, triangle = Case 3, inverted triangle = Case 4, diamond = controls.

significant abnormality in the corresponding OEF, were subsequently selected in order to obtain a sample of 'pure metabolic depression' and to exclude any instance of metabolic depression mismatched from CBF (i.e., luxury perfusion and misery perfusion) (Baron, 1985).

There were 24 such ROIs, found in 3 of the 4 patients. In this sample, the mean ($\pm$1 SD) CBV (2.10$\pm$0.83 ml·100 ml^{-1}) was significantly lower than in the controls (3.19$\pm$0.66 ml·100 ml^{-1}, n = 186 ROIs) by comparison of means (F test, $P<0.001$).

In order to investigate in further detail the pathophysiology of this decrease in CBV in pure metabolic depression, areas with less severe metabolic depression (i.e., rCMRO$_2$ asymmetry within 0-1 and within 1-2 SD of controls, but still without significant alteration in OEF) were also analysed. There were 56 such ROIs in addition to the original 24. In order to compress this large number of

ROIs, all the ROIs belonging to each of the above-defined 3 domains (i.e., 0–1, 1–2, and >2 SDs) were averaged for each patient, yielding 2 or 3 such average values per patient. In fig. 2A and B the percentage asymmetries in CBV are plotted as a function of the corresponding asymmetries in CBF and $CMRO_2$, respectively, calculated for these average values. These graphs demonstrate that the decrease in CBV which accompanies pure metabolic depression is linearly dependent on the severity of the latter ($P<0.02$ and $P<0.05$ for CBF and $CMRO_2$, respectively).

The same analysis was applied to the rt values in pure metabolic depression: the mean t (±1 SD) was not different from controls (0.095±0.02 min and 0.090±0.02 min, respectively), and its asymmetry was not correlated with the CBF or $CMRO_2$ percentage asymmetry values.

Carotid occlusion (group II, n = 4)

Our goal in this sample was to investigate the interrelationships of local CBF, CBV and t as a result of reduced cerebral perfusion pressure. However, the above demonstration of a reduction in CBV in areas with metabolic depression led us as a first step to exclude from analysis the ROIs with a statistically significant decrease in $CMRO_2$ because of the possible interference with the phenomenon studied. This caused exclusion of all ROIs from Case 8 in whom there was a conspicuous metabolic depression affecting the entire cerebral cortex on the side of the occluded carotid artery, and exclusion of 0, 2 and 3 ROIs with significant $CMRO_2$ asymmetry in Cases 5, 6 and 7, respectively. For each patient, the ROIs were grouped as 'occluded side' and 'patent side'. As in control subjects, there were significant positive linear correlations between CBV and CBF in each patient on the occluded as well as on the patent side, with negligible intercepts (Table 3; fig. 3A); the slopes found were steeper on the occluded than on the patent ($P<0.025$) side, but the slopes on both the occluded and the patent side were significantly ($P<0.02$) larger than the control slopes (shown in Table 2) (nonparametric Kruskal-Wallis H test). Compared with control data (fig. 1A) it is also clearly apparent that very high regional CBV values (despite relatively low CBF values) were present in each occluded territory, while this effect was less obvious on the patent side. The CBV in the occluded side was significantly higher

TABLE 3. LINEAR REGRESSION OF rCBV ON rCBF IN CASES 5, 6 AND 7

	Case	*Slope ± SD*	*Intercept (ml · 100 ml⁻¹)*	*n*	*r*	*P*
Patent side	5	0.136±0.024	−1.90	19	0.81	< 0.01
	6	0.109±0.014	+0.24	14	0.92	< 0.01
	7	0.118±0.027	−0.80	12	0.81	< 0.01
Occluded side	5	0.148±0.022	+0.01	19	0.86	< 0.01
	6	0.197±0.024	−1.04	14	0.92	< 0.01
	7	0.216±0.046	−2.87	12	0.83	< 0.01

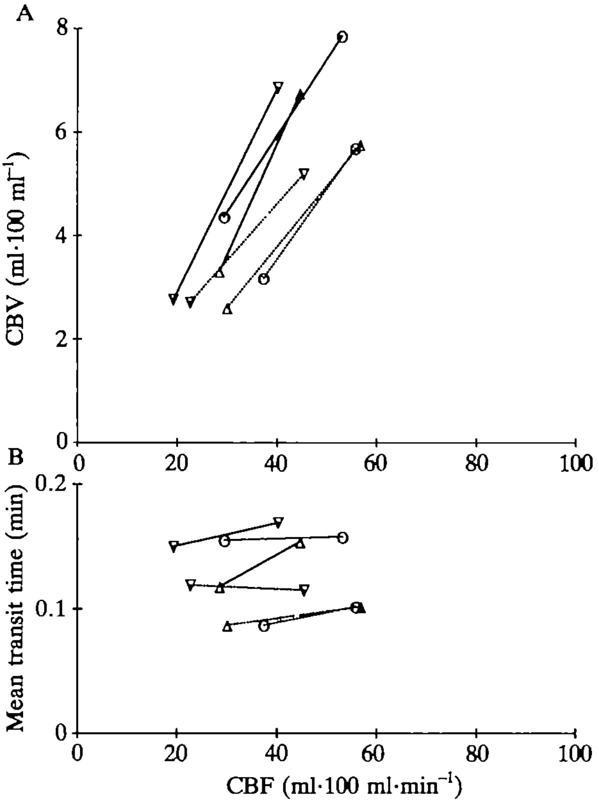

FIG. 3. Linear correlations between rCBV and rCBF (A) and between rt and rCBF (B) in grey matter regions of *Cases 5, 6* and *7* with unilateral carotid artery occlusion, shown separately for the occluded (continuous line) and for the patent side (broken line). For easier identification each patient's lowest and highest rCBF values are shown. In every patient, the rCBV-rCBF relationship on each side was statistically significant; for the rt-rCBF correlations, none was significant. Compare the slopes for a similar analysis in control subjects (fig. 1A, B). Circle = Case 5, triangle = Case 6, invented triangle = Case 7.

than that on the patent side for each patient ($P<0.01$, 0.05 and 0.01 for Cases 5, 6 and 7, respectively; paired t test).

As in the control subjects, the mean rt was not linearly correlated with CBF in any patient and any hemisphere (fig. 3B), but the mean t on each occluded side was significantly higher than that on the homologous patent side ($P<0.001$ by paired t test) for each patient. Also the average mean rt on the occluded, but not on the patent side (n = 3) was significantly higher than the control value (n = 5) (mean ± 1 SD; 0.146 ± 0.012 min, 0.102 ± 0.013 min and 0.090 ± 0.012 min, respectively; $P<0.02$, nonparametric Kruskal-Wallis H test).

Graphic representation of regional haemodynamic failure

The ratio CBF/CBV was determined in our patients and analysed in relation to other variables to explore further the suggestion that this ratio provides an index of local cerebral perfusion pressure (Gibbs *et al.*, 1984; Powers *et al.*, 1987). Our sample of patients includes 3 very illustrative cases: (1) Case 5 had a unilateral carotid occlusion and postocclusive transient ischaemic attacks unresponsive to anticoagulation or antiplatelet agents; her PET scan showed a widespread 'pure' misery perfusion on the occluded side, that is, without metabolic derangement; (2) Case 8 had a unilateral internal carotid artery (ICA) occlusion heralded by orthostatic transient ischaemic attacks and followed by a minor stroke with continuing orthostatic events; her PET scan showed on the occluded side a widespread misery perfusion, superimposed on a conspicuous diffuse $CMRO_2$ depression; (3) Case 9 had a left hemisphere embolic stroke which recovered almost completely in a few days and left only questionable sequelae on the CT scan (a slightly widened sylvian fissure); his PET scan performed 30 h after onset showed an extremely severe focal misery perfusion ($OEF > 0.80$) with a moderate reduction in $CMRO_2$. These 3 cases offer the opportunity of investigating the whole spectrum of oligaemia and ischaemia (*see* Introduction), from preserved to reduced $CMRO_2$, including within-patient regional gradients of severity.

The rOEF is plotted in fig. 4 as a function of the rCBF/rCBV ratio in the ROIs

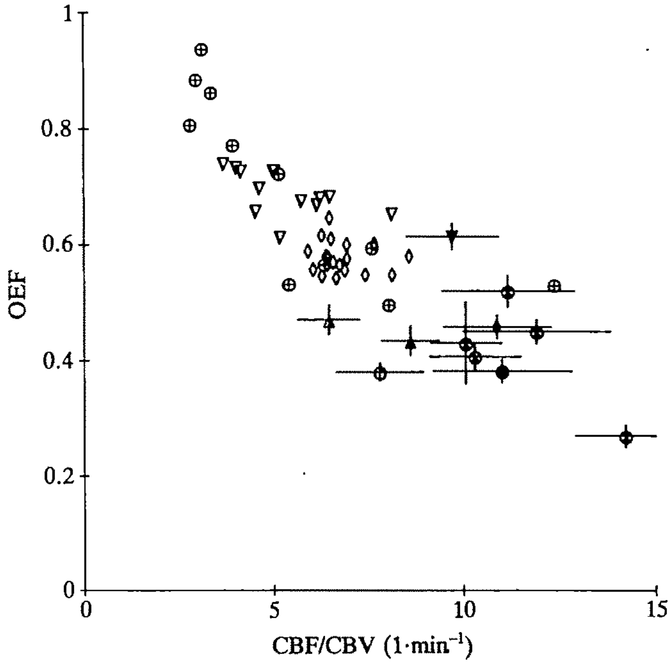

FIG. 4. Plot of rOEF as a function of the rCBF/rCBV ratio in various regions of the affected hemispheres of *Cases 5* and *8* (internal carotid artery occlusion) and *Case 9* (acute ischaemic stroke); for comparison, the corresponding mean (±SD) values are shown for the patent hemispheres of *Cases 5* to *8*, and for each one of the 5 control subjects. ⊗ = Controls (mean ± SD); Case 5, ◆ = patent (mean ± SD), ◇ = occluded (regional values); Case 6, ▲ = patent (mean ± SD), △ = occluded (mean ± SD); Case 7, ● = patent (mean ± SD), ○ = occluded (mean ± SD); Case 8, ▼ = patent (mean ± SD), ▽ = occluded (regional values); Case 9, ⊕ = ischaemic hemisphere (regional values).

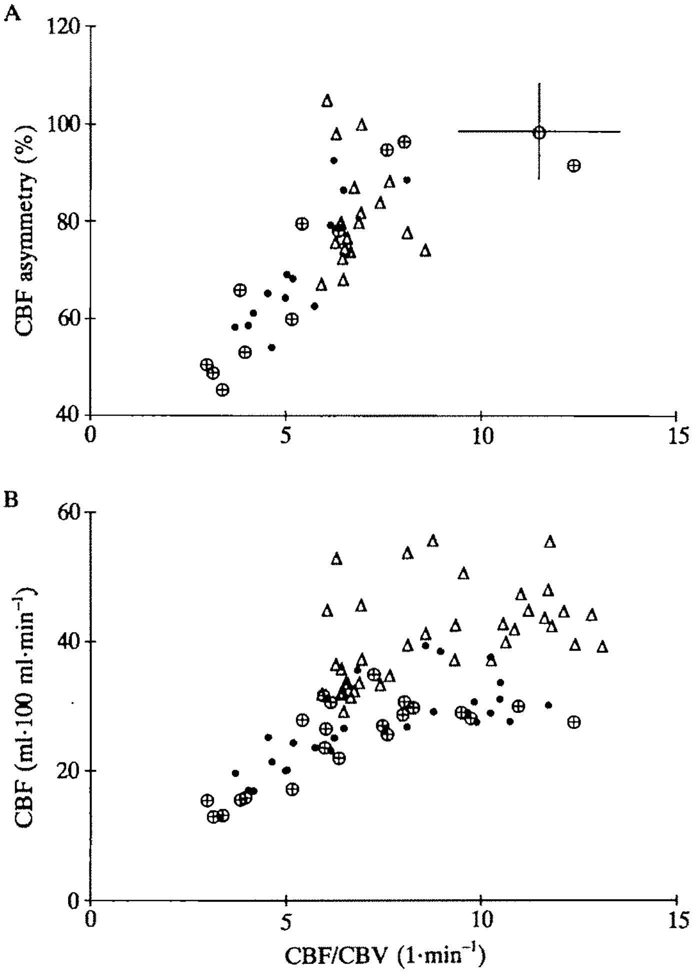

FIG. 5. Plot of rCBF percentage asymmetry (A) and absolute (B) values as a function of the corresponding regional CBF/CBV ratio, an index of the CPP, in 3 patients with 'misery perfusion' of graded severity (no metabolic effect in *Case 5*, rCMRO$_2$ decrease in *Cases 8* and *9*). For comparison, the corresponding mean ($\pm$ 1 SD) values of 5 control subjects are also shown in A. There is a roughly linear reduction of rCBF with falling CBF/CBV ratio below a critical ratio of about 7·min^{-1}, depicting the expected relationship between local flow and perfusion pressure below the lower limit of autoregulation. Triangle = Case 5, closed circle = Case 8, crossed circle = Case 9.

of the ischaemic hemisphere of these 3 patients; for comparison, this figure also gives the means ± 1 SD for the corresponding values in the 5 controls, in the patent carotid territory of the 4 patients with carotid occlusion (Cases 5–8), and on the occluded side of Cases 6 and 7. This graph, constructed according to Gibbs *et al.* (1984), confirms the progressive rise of the rOEF as the CBF/CBV ratio falls and the reduction in the latter ratio in patent and even more in occluded territories compared with control subjects.

Fig. 5A and B shows the rCBF percentage asymmetry (A) and absolute (B)

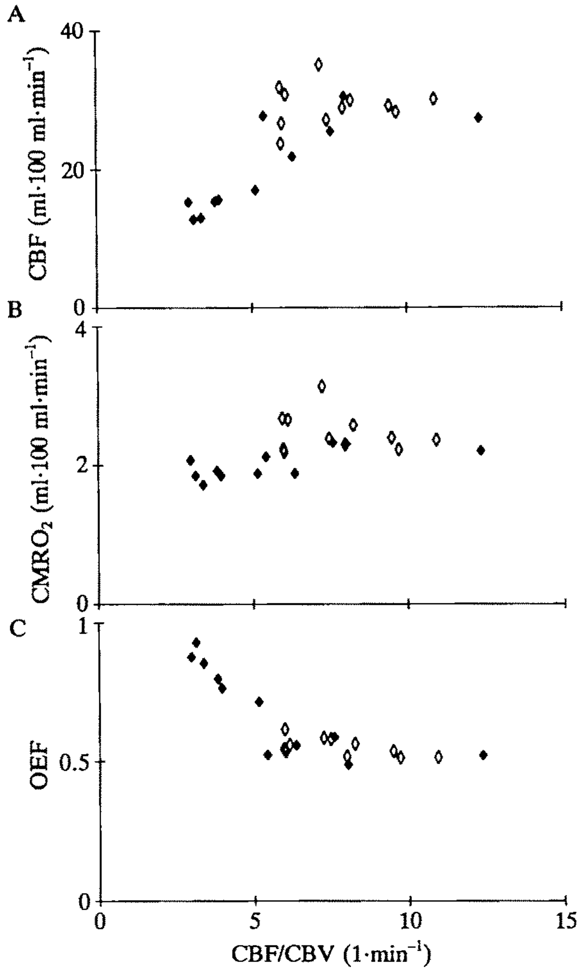

FIG. 6. Plot of rCBF (A), rCMRO$_2$ (B), rOEF (C) as a function of the rCBF/rCBV ratio in cortical regions of the affected and the contralateral hemispheres of *Case 9*; comments as in figs 4 and 5. In addition, this graph shows a moderate rCMRO$_2$ decline only at levels of rCBF/rCBV at which the rCBF is markedly reduced and the rOEF markedly elevated. Open diamond = contralateral side, closed diamond = affected side.

values as a function of the corresponding rCBF/rCBV ratio of Cases 5, 8 and 9 compared with the corresponding mean values found in controls. This graph shows a fall in rCBF as the rCBF/CBV gradually decreases below a consistent threshold value of ~ 7·min^{-1} (~65% of control value).

Fig. 6 strikingly illustrates in the whole set of cortical ROIs (both hemispheres) of a single patient (Case 9), the changes in rCBF and rOEF just described, as well as those—not previously shown—in rCMRO$_2$, as a function of the rCBF/rCBV ratio. The expected reduction in rCMRO$_2$ in the ischaemic hemisphere is only moderate and occurs at rCBF/rCBV ratio values well below those necessary to affect the rCBF.

In fig. 7, the rCBV is plotted as a function of the CBF/CBV ratio in Cases 5, 8 and 9 separately. In order to distinguish the effects of pure haemodynamic failure (as exemplified by Case 5) from those of superimposed reduced rCMRO$_2$,

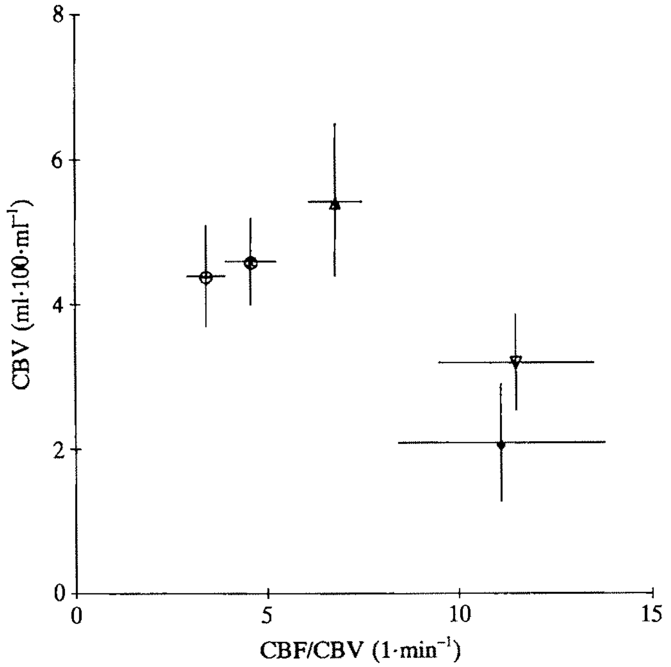

FIG. 7. Plot of mean CBV (±1 SD) as a function of the CBF/CBV (±1 SD) ratio in the 5 control subjects, the cortical areas with significant pure metabolic depression of group 1 patients, the areas with significant pure misery perfusion of *Case 5* (occluded side), and the areas with misery perfusion superimposed on significant metabolic depression of *Cases 8* and *9* (affected sides). This graph shows (1) the significant decrease in rCBV in pure metabolic depression at normal CBF/CBV ratio; (2) the maximal increase in rCBV in pure misery perfusion; and (3) the significant trend for decreasing rCBV as the CBF/CBV ratio falls further, in association with metabolic impairment, reflecting the effects of the prevailing metabolic rate on the vasomotor tone of the cerebral vasculature both at normal and at very low CPP. Chronic misery perfusion with metabolic depression (⊗), acute misery perfusion with metabolic depression (⊕), pure misery perfusion (▲), pure metabolic depression (◆), controls (▽).

only the ROIs from Cases 8 and 9 with a significant decrease in rCMRO$_2$ (asymmetry index > 2 SDs from controls) were selected. In each of these 3 patients, the selected ROI values were clustered around similar CBF/CBV values and only the mean (±1 SD) values are shown. For comparison, the corresponding overall mean value for the controls as well as for areas with significant decrease in CMRO$_2$ of patients of group I (pure metabolic depression) are also shown. This graph shows an increase in rCBV as the CBF/CBV ratio falls, maximal in Case 5 ('pure' misery perfusion), with a lesser increase in rCBV as this ratio falls further ($P < 0.02$ by comparing the data of Cases 8 and 9 with those of Case 5).

DISCUSSION

Methodological issues

In this study, the CBV has been measured using the C^{15}O continuous inhalation technique (Subramanyam *et al.*, 1978). This method had not been implemented until recently (Pantano *et al.*, 1985) for fear of CO toxicity. However, we have designed a labelling procedure which is essentially carrier-free (Pantano *et al.*, 1985), as demonstrated by the fact that after 7 min of tracer inhalation, the mean percentage carboxyhaemoglobin (relative to haemoglobin) in arterial blood in subjects was 1.6% ±0.88, the highest value being 4.0%, all well below acute toxicity levels (Chinn, 1949).

Purity of $C^{15}O$ is essential if accurate measurement of CBV is desired (Martin *et al.*, 1987). We always found <0.2% of whole blood radioactivity present in plasma, indicating no significant contamination from $C^{15}O_2$. The equation used for derivation of regional CBV (Eq. 1) contains the parameter ρ, the brain-to-peripheral haematocrit ratio, for which we chose a constant value of 0.85, in agreement with most investigators (Phelps *et al.*, 1979; Yamaguchi *et al.*, 1986; Martin *et al.*, 1987). Lammertsma *et al.* (1984) have estimated this ratio at 0.70 in the normal human brain, but this finding has not been replicated as yet. Although ρ is essentially uniform in normal brain (Lammertsma *et al.*, 1984), regional variations probably occur in focal brain ischaemia, but the resultant errors are acceptable (an increase of 10% in the true ρ value in slowly perfused tissue would result approximately in a 10% overestimation in measured CBV). Equation 1 also shows that the measurement of CBV depends on knowledge of CBF, which was measured in our study by the steady-state $C^{15}O_2$ method (Frackowiak *et al.*, 1980); however, propagation of the errors in the determination of CBV are limited because the ratio Ca/Ct is typically much larger than the ratio λ/CBF. For example, an underestimation in measured rCBF of 20% would result in an overestimation in rCBV of about 0.3% for typical values of 40 $ml \cdot 100\ ml^{-1} \cdot min^{-1}$ and 4.7 $ml \cdot 100\ ml^{-1}$, respectively. The ranges of rCBV values found in our 5 control subjects are consistent with previously published PET data obtained with single-breath or 1 min inhalation of either $C^{15}O$ or ^{11}CO (Grubb *et al.*, 1978; Phelps *et al.*, 1979; Lammertsma *et al.*, 1983; Yamaguchi *et al.*, 1986; Perlmutter *et al.*, 1987; Pozzilli *et al.*, 1987), supporting the validity of our method. However, regardless of the method used, some discrimination in the selection of the regions of interest is required when analysing CBV images in order to avoid the brain areas located close to large vascular pools (*see* Methods) as spuriously higher CBV values would otherwise obtain (Martin *et al.*, 1987). We chose this CBV method because it is ideal for correction of the measured OEF for nonextracted intravascular $^{15}O_2$ labelled haemoglobin in the steady-state procedure (Lammertsmá *et al.*, 1983; Pantano *et al.*, 1985). In this approach the $^{15}O_2$ scan is directly corrected whereas in the classical method (Lammertsma *et al.*, 1983) the uncorrected OEF image is obtained first and then corrected by means of the corresponding CBV and CBF images, allowing for larger error propagation. In addition, the classical OEF correction method, but not our approach, is dependent on the local cerebral haematocrit (Lammertsma *et al.*, 1987).

Results in controls

We found that the rCBV, measured in various cortical areas, was positively correlated with the corresponding rCBF in each of our 5 control subjects, with little intersubject variability in the calculated slopes, and an overall intercept close to zero (fig. 1A, Table 2). There are no similar data from human controls in the open literature to allow comparison with our findings. Using a different method, Grubb *et al.* (1974) found in monkeys that the whole brain CBV was related to the corresponding CBF according to the relationship $CBV = 0.8\ CBF^{0.38}$. The mean CBV values measured in our 5 control human subjects fall within 3.7% (±2.5%,1 SD) of those expected from the relationship of Grubb *et al.*, an indirect validation of our methodology.

This relationship between CBV and CBF is consistent with the notion that both capillary density and rCBV are lower in white compared with grey matter (Campbell, 1938; Lammertsma *et al.*, 1983, 1985). In addition, the interpretation of this correlation between rCBV and rCBF is illuminated by the fact that similar positive correlations were found for the rCBV-$rCMRO_2$ relationship, while the rt value was essentially independent of either rCBF or $CMRO_2$ (fig. 1B). This indicates that the regional pattern of CBV in controls reflects the normal perfusion-metabolism couple (Raichle *et al.*, 1976; Lebrun-Grandié *et al.*, 1983) at constant cerebral perfusion pressure. Hence, according to classical views on the mechanism of this physiological regulation (Siesjõ, 1984), the local variations in $rCMRO_2$ that characterize the normal brain would, by largely unknown biochemical and/or neuronal mechanisms, result in proportional changes in local vascular tone and, in turn, in both rCBV and rCBF.

Pure metabolic depression

In this study, one of our interests was to distinguish haemodynamic from metabolic factors in the rCBV changes observed in cerebral ischaemia. To this end, we first studied the effects of pure metabolic depression (PMD) or rCBV in 4 patients with subcortical stroke (known frequently to induce ipsilateral cortical hypometabolism; *see* Feeney and Baron, 1986), and free of significant cervical arterial disease. We found that PMD was associated with a significantly reduced CBV, and that the percentage reduction in both rCBF and $rCMRO_2$ was attended by a proportional and similar reduction in rCBV (fig. 2A, B). The use of the asymmetry index was meant to distinguish the rCBV-$rCMRO_2$ relationship in PMD from that present in normal subjects, as it cancels out the effects on rCBV both of the normal intrasubject variability in $rCMRO_2$ and of the intersubject variability in age and physiological parameters (e.g., $PaCO_2$, haematocrit). The lack of significant change in rt in PMD (expected from the clinical selection criteria) suggests that the reduction in rCBV occurred without alterations in cerebral perfusion pressure. On the whole, therefore, our data demonstrate that the reduction in metabolic activity in the deafferented cortex leads to a 'metabolic vasoconstriction', by virtue of the perfusion metabolism coupling phenomenon, the preservation of which characterizes PMD. Other explanations for our findings appear unlikely; hence incomplete infarction in the affected cortex, undetected by CT or MRI, can be excluded with reasonable confidence (*see* Feeney and Baron, 1986), while reduction of the capillary bed as an adaptation to depressed metabolism, if at all, would presumably only result in minimal changes in the measured CBV (Lammertsma and Jones, 1983).

Carotid occlusion and regional haemodynamic failure

To study the effects of haemodynamic factors on the measured variables, we selected 4 patients with longstanding unilateral carotid artery occlusion, in whom the entire spectrum of haemodynamic failure was represented, from no significant effects on rCBF (Cases 6, 7) and pure misery perfusion (reduced rCBF but preserved $rCMRO_2$ Case 5), to combined misery perfusion-metabolic depression (reduced rCBF and $rCMRO_2$, increased OEF, Case 8). To investigate this spectrum further, we also included Case 9 who displayed an area of extremely severe misery perfusion with metabolic depression in the context of an acute embolic stroke.

In contrast to previous studies (Gibbs *et al.*, 1984; Powers *et al.*, 1987), our approach in this patient sample was to analyse the phenomena in individual ROIs in order to evaluate the reliability of PET both on a *regional* basis, and in single patients.

In the ROIs without metabolic impairment, we confirmed the significant increase both in rCBV and rt on the occluded compared with the patent side, previously reported by Gibbs *et al.* (1984) and Powers *et al.* (1984, 1987). On a regional basis, although rCBV and rCBF were linearly correlated as in controls, the slopes were significantly steeper on the occluded than on the patent sides, and on the patent sides than in control subjects, indicating that, in unilateral internal carotid artery occlusion, the regional coupling between CBV and CBF may be altered on *both* sides as a result of reduced cerebral perfusion pressure (CPP). Clearly, the use of average hemisphere values would have overlooked these regional effects, and the use of the occluded/patent carotid territory ratios would have underestimated the real increase in CBV on the occluded side as a result of the contralateral haemodynamic 'steal'.

In our further analysis of haemodynamic failure, extended to brain regions with metabolic impairment, we chose to evaluate the CPP by means of the rCBF/rCBV ratio. Gibbs *et al.* (1984) have suggested previously that this ratio is a sensitive index of, and monotonously decreases with, the CPP. Fig. 4, designed after these authors, documents the progressive rise of rOEF with declining rCBF/rCBV ratio while less severe reduction in this ratio occurred in chronically occluded internal carotid artery territories and contralateral territories, as compared with control values. These findings strongly support Gibbs' proposal that the CBF/CBV ratio can be used as an index of CPP, and show that this type of analysis can usefully be extended to individual brain regions in single patients. The apparent 'critical' CBF/CBV ratio at which the OEF starts to rise is about 6–7 min^{-1}, consistent with Gibbs *et al.* (1984). From fig. 4, however, it appears that the elevation of the regionally measured OEF is actually a rather gradual process, as also observed recently by Kanno *et al.* (1988) and in agreement with the smooth lower end of CBF autoregulation (MacKenzie *et al.*, 1979). On the basis of these findings, therefore, we would disagree with the conclusions of Powers *et al.* (1985*b*) and Itoh *et al.* (1987) that the CBF/CBV ratio is not a sensitive indicator of perfusion reserve. As shown by Gibbs *et al.* (1985), methodological problems in the measurement of the parameters probably partly explain these discrepancies. Hence, the relationship between rCBF/rCBV and rOEF, shown in fig. 4 for essentially intact brain tissue, is most likely disrupted in necrotic tissue or cavitated infarcts, where the assessment of CPP by the CBF/CBV ratio may be erroneous (Powers *et al.*, 1985*b*; Itoh *et al.*, 1987).

These favourable features of the CBF/CBV ratio allowed us to consider the behaviour of each of its components, namely rCBF and rCBV, as CPP falls. Fig. 5A and B show a roughly linear decline in rCBF, as measured in individual ROIs of Cases 5, 8 and 9, at values of rCBF/rCBV below the consistent critical value of about $6\text{–}7 \cdot \text{min}^{-1}$ ($\sim$65% of the normal ratio), consistent with the well-described phenomenon of CBF autoregulation (MacKenzie *et al.*, 1979). In addition, this critical value of the rCBF/rCBV ratio is strikingly similar for rCBF and for rOEF (*see* fig. 4). These interrelationships among CBF, OEF and CPP are shown here in different brain regions of individual patients, with the distinct advantage that the CPP is estimated locally and not extrapolated from the measurement of the systemic arterial pressure. This is strikingly illustrated in fig. 6, which documents in a single patient the behaviour of rCBF, rOEF and $rCMRO_2$ as local perfusion pressure gradually falls from the contralateral hemisphere to the ischaemic core, where depressed metabolic rates are apparent. Until now, these interrelationships among local CBF, OEF, $CMRO_2$ and CPP had been represented only in idealized fashion (*see* Powers and Raichle, 1985).

What are the effects of superimposed metabolic depression on the haemodynamic reserve? The latter can be assessed either by measuring the *maximal* response of CBF to brain vasodilatation induced by hypercapnia or acetazolamide (Brown *et al.*, 1986; Vorstrup *et al.*, 1986; Kanno *et al.*, 1988), or by evaluating the *maximal* vasodilatation induced by systemic hypotension (MacKenzie *et al.*, 1979). These methods were not used here, but the combined measurement of baseline CBV and CBF permits the analysis of the factors intrinsic to the haemodynamic reserve. In this respect, fig. 7 shows several interesting features. First, the situation of pure misery perfusion (exemplified by Case 5) is associated with an extremely high CBV as a result of critically reduced CPP, signalling the limit of haemodynamic reserve (the OEF on the occluded hemisphere was around 0.53, a value at which the cerebral vasodilatory capacity is exhausted according to Kanno *et al.*, 1988). Secondly, the study of the cortical areas of Cases 8 and 9, both of which exhibited reduced $CMRO_2$ and notably increased OEF, revealed a significant tendency for rCBV to return towards normality as CPP falls to very low levels.

A similar lessening in cerebrovascular vasodilatation, as measured by the diameter of pial arteries, was observed by MacKenzie *et al.* (1979) in cats at extreme systemic hypotension. We suggest that, in addition to mechanical vascular collapse and the hypothetical release of vasoactive substances by ischaemic tissue, the metabolic depression of cerebral ischaemia also directly contributes to this phenomenon, based on three lines of argument. (1) Pure metabolic depression, although of a different nature than ischaemic hypometabolism, and occurring at normal levels of CPP, also induces a 'metabolic vasoconstriction', as depicted in figs 2 and 7. (2) The critical systemic arterial pressure for maximal vasodilatation in the experiments of MacKenzie *et al.* (1979) was identical to that found for electrophysiological failure in the same animals (Gregory *et al.*, 1979). (3) Hypothermia, which is known to reduce $CMRO_2$, shifts the lower limit of CBF autoregulation to lower values of CPP (Donegan *et al.*, 1985), as does hypocapnia (Ekström-Jodal *et al.*, 1971/1972), both presumably by increasing the baseline vascular tone. If the cerebrovascular tone is indeed partly regulated by PtO_2, the oxygen tissue partial pressure (Kontos and Wei, 1985), then the depression of oxidative metabolism that characterizes neuronal ischaemia would tend to revert the existing (maximal) vasodilatation by reducing the imbalance between oxygen supply and demand and, in turn, improving the PtO_2. The above described process would serve to regenerate some haemodynamic reserve at very low CPP levels, a mechanism perhaps involved in the protection against cerebral ischaemia afforded by hypothermia or barbiturates (Astrup, 1982). Gregory *et al.* (1979) noted that the EEG flattens for higher CPP values in the unanaesthetized than the anaesthetized animal during systemic hypotension. Takano *et al.* (1988) indicate that in the deafferented cortex following capsular stroke, the CBF reactivity to hypercapnia is considerably larger than in the surrounding normal cortex suggesting that, at variance with the classical work of Fujishima *et al.* (1971), reduced neuronal activity may increase the vasodilatory capacity of the cerebral vessels. This mechanism would perhaps help explain the recent experimental observation of Strong *et al.* (1988) that the CBF response to cortical electrical stimulation in the 'ischaemic penumbra' is reduced but not completely abolished. Taken together, therefore, the depression of energy metabolism during ischaemia, by its simultaneous effects on CBV and on OEF, may have some protective effects in critical conditions of oxygen delivery.

This study clearly documents the sensitivity of PET in cerebrovascular pathophysiological research by assessing simultaneously and regionally the haemodynamic and metabolic variables in the brain of individual patients.

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CROSSED APHASIAS CAN BE MIRROR IMAGE OR ANOMALOUS

CASE REPORTS, REVIEW AND HYPOTHESIS

by MICHAEL P. ALEXANDER, MARIA R. FISCHETTE,
and RICHARD S. FISCHER

(*From the Aphasia Program, Braintree Hospital, and Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA*)

SUMMARY

Individual cases of crossed aphasia (aphasia after a right hemisphere lesion in a right-hander) have often been reported. A number of theories have been proposed as to the neuropsychological and/or neurobiological mechanisms that might underlie this phenomenon, but there is still disagreement about its language phenomenology and possible significance. We report 2 cases of crossed aphasia after stroke and review 34 cases from the literature with anatomical documentation of lesion site. Analysis of this material suggests that they represent at least two populations. There may be general conclusions concerning mechanisms of cerebral lateralization to be learned from the investigation of anomalous groups such as crossed aphasics.

INTRODUCTION

Aphasia in a dextral following a lesion of the right hemisphere (crossed aphasia) is rare. Although estimates vary, the incidence is probably between 1 and 2% of all dextral aphasics (Gloning *et al.*, 1969). The neurobiological mechanisms of this phenomenon are unknown, and the neuropsychological correlates are only incompletely understood. We report 2 cases of dextrals with crossed aphasia. One patient had an entirely anomalous aphasia profile; the other had entirely appropriate *intrahemispheric* syndromes, although in the 'wrong' hemispheres. Detailed evaluation is reported both of spoken and written language, as well as for other cerebral functions which are commonly held to be strongly lateralized. Cases in which there is dissociated lateralization of cerebral functions which are usually anatomically linked may illuminate the basic mechanisms of lateralization. Review of the recent literature on this subject suggests some plausible neuropsychological correlations.

Correspondence to: Dr Michael P. Alexander, Braintree Hospital, 250 Pond Street, Braintree, MA 02184, USA.

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CASE REPORTS

Case 1

The subject is a 54-yr-old man. He holds a Master's degree and before his illness was employed as an engineer. He speaks only English. He is fully right-handed; for 8 of 8 unimanual tasks (e.g., shaving, throwing a ball, etc.) he indicated a strong right hand preference. One (a son) of 9 primary relatives is left-handed. The patient had no previous neurological history. In January, 1987 he suffered a right hemisphere vascular lesion resulting in fluent aphasia and a left hemiplegia. He was referred to Braintree Rehabilitation Hospital. We examined him at 2½ wks, 15½ wks and 11 months after his stroke.

Neurological examination revealed a severe left hemiparesis, moderate left-sided sensory loss primarily affecting the face and hand, and no visual field defect or hemifield neglect to double simultaneous stimulation. There were no impairments of articulatory agility, speech prosody (including affective elements) or voice volume. Neurological examination of the right half of the body was entirely normal.

Language examination

Spontaneous output was fluent and grammatical but very empty, with much phonemic, neologistic and extended English jargon. When asked why he was in hospital, he replied 'Vaguely it happened without sustenance . . . on a Thursday . . . Friday, no a . . .'. Asked about his work he said, 'Outlining the facon . . . facilities . . . whether it was all retick or all rentricles, but she does not seem to be producing what is going in'.

Auditory comprehension was impaired. The patient correctly pointed to named or described objects before him on a table (10/12). He had difficulty matching parts of objects to their names (6/10). He matched objects to a one sentence functional description (6/6). Body part name matching (11/12) and colour name matching (6/6) were good. He carried out 4/5 one-step commands with objects ('Hand me the comb'). He was unable to follow any more complex commands. Responses to simple yes/no questions were correct, but performance decreased as complexity and length increased. Comprehension of explicitly grammatical material was at chance level.

Naming was very poor (2/7 common objects, no parts of objects, and 2/10 body parts) with perseveration and bizarre responses. The following sample represents a string of 5 body parts that he was asked to name: nose, 'nose'; knee, 'right-handed nose'; shoulder, 'balanced eagle'; (cue; sho . . .), 'shoulder pad'; hair, 'I don't know'; (cue: ha . . .), 'hair'; thigh, 'logging pad'.

Repetition was normal except for occasional bizarre substitutions on the longest items. Recitation was normal. The patient was able to sing with good melody but with paraphasic lyrics.

Narrative writing using the preferred right hand showed preserved orthography, fluency, and paragrammatism. The content was perseverative jargon. The following is his written description of the Cookie Theft picture:

> Joe Paris is relevealed us of new olding apive which is redgiving is for us on the ricewater us to being giving on the board board stararts. The bying is berried to by going in unside. His is unsunang, us of here hering herrings. The herrist horisting.

Writing to dictation was typical of phonological agraphia (Roeltgen *et al.*, 1983).

Reading aloud was paralexic and deteriorated with length. On the Boston Diagnosis Aphasia Examination (Goodglass and Kaplan, 1983) scores were: symbol-word recognition 9/10, word picture match 8/10, sentence-paragraph comprehension 3/8. Output included semantic and phonemic paralexias as well as extended English jargon. Reading comprehension was adequate at the single word level, but worse than auditory for longer material.

Neuropsychological examination

Ideomotor praxis. Buccofacial and right arm praxis to command were normal. Visuospatial abilities appeared nearly intact. The patient was able to copy simple and complex geometric designs with no evidence of left-sided neglect. On line bisection he bisected each line normally and worked from left to right. Map Orientation was intact (13/14), as was right/left orientation. His scaled score on the Block Design subtest of the Wechsler Adult Intelligence Scale-Revised was 8 (age-scaled score was 9). On Judgement of Line Orientation he achieved an age corrected score of 24 which places him in the average range. Copying the Rey-Osterrieth Complex Figure was well organized and integrated, as was his copy of the geometric figures of the Wechsler Memory Scale (Visual Reproduction). In contrast, however, his immediate memory of the figures was poor (4/14 details), reflecting such errors as loss of specific internal details and misplacement of single elements. In a 30 min delayed condition, his productions were marred by the intrusion of details from one design into another which resulted in a figure that was a conglomeration of the others.

Attention. Attention and concentration were normal during clinical testing. He was able to maintain his effort and energy and showed no motor impersistence. Visual span of attention was 5 forwards and 4 backwards (Corsi Block Test). On Trails A, he was able to connect the alternating numbers fairly well although his time was rather slow (85 s). Perseveration was prominent throughout.

Affect. Prosody and facial expression were normal.

Emotion. The patient was aware of his deficits but remained unconcerned and unrealistically optimistic. Insight into the implications of his disability seemed reduced despite discussion of his limitations.

Course

When reevaluated at 15 wks postonset, the basic profile described above was unchanged. Spontaneous narrative output showed a less severe jargon aphasia; the major limitation to communication was word finding difficulty. Asked about his major activities, he responded 'Three days of the week I go to the Phys Ed area. I get some . . . some . . . and I get a little training there. The girl there teaches me to . . . what do you call it? Barbara does the . . . (gestures range of motion with his hand). Barbara still is nursing the hand. I still can't get any louse out of the hand. The right shoulder is fine. I just don't have any inkwince for the right foot (he meant the hand). And that's about what I've been doing.' Auditory comprehension was slightly improved. Perseveration was less prominent. Insight was still impaired although the vocational implications of his hemiparesis seemed clearer to him.

When examined at 11 months after onset, he had shown additional interim improvement. Spontaneous output was much less paraphasic. He described the 'Cookie Theft Picture' (Goodglass and Kaplan, 1983) with 'The boy is . . . uh . . . in a chair reaching for a cookie and he's going to fall. The girl is waiting for him also. In the other (gestures to the side) . . . on the kitchen table the wife is drying the dishes but the . . . the sink is flowing over . . . flowing over and the dishes uh . . . uh . . . uh . . . they're running over.' Responsive conversation was also largely free of paraphasias. Confrontation naming and auditory comprehension were equally improved. Writing remained extremely paraphasic and perseverative. His written description of the same picture went 'The boy is gotting the spoon cookie jarried the boy is getteing. The girl commed the the cookies. The wife is cutting the wiffing the water is cutting overed.'

CT findings

CT showed a large frontal opercular and perirolandic cortical and subcortical infarct (fig. 1). There was also an extensive lesion in the putamen. The left occipital lobe was longer than the right, and the right frontal lobe was longer than the left. This is the most common profile of CT asymmetries in right-handed men and is considered 'typical' (Koff *et al.*, 1986).

Summary

To infer from the profile of deficits after his right brain injury, this patient has a mixture of anomalous lateralizations. The severe language deficit—both spoken and written—after right brain

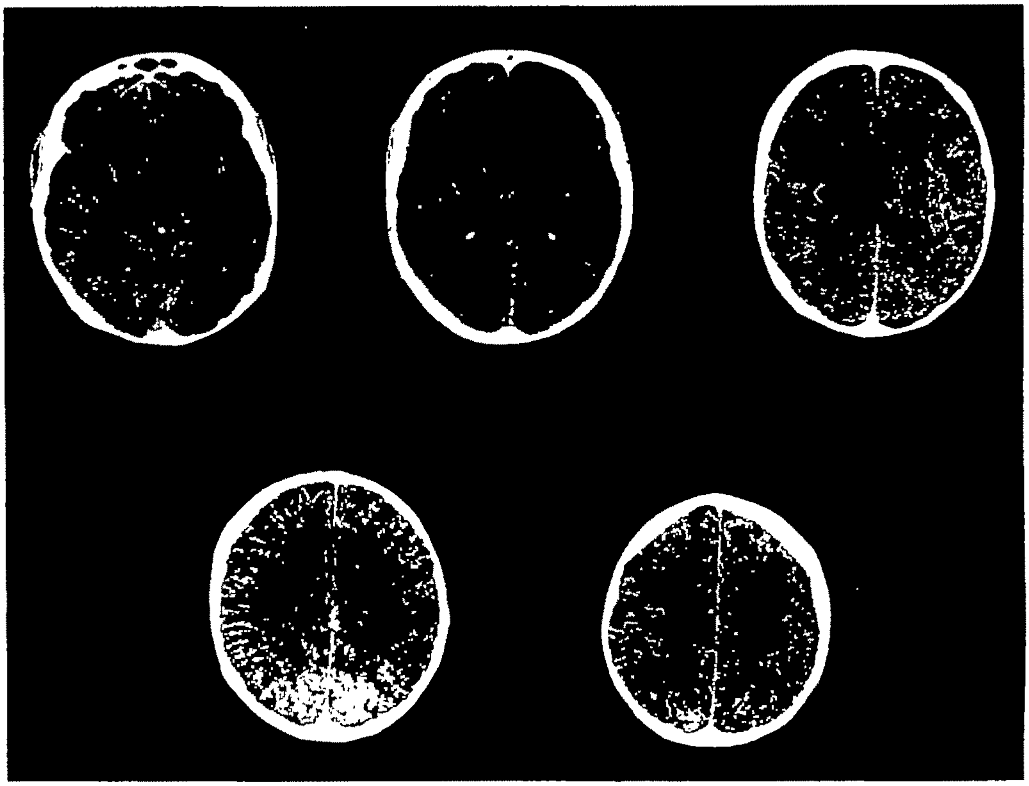

FIG. 1. CT scan of *Case 1* performed 9 months after onset. The structures involved by the lesion are discussed in the text.

injury is, of course, anomalous, and constitutes crossed aphasia. The absence of any ideomotor apraxia is not surprising after right brain injury in a right-hander. The absence of any left hemifield neglect and of configurational difficulties with complex constructional tasks is anomalous after a right brain lesion of the size of this case. The unrealistic optimism and cheerfulness may be an expected effect of major right frontal damage.

Some authors would have rejected this patient for study because of his left-handed son (Joanette *et al.*, 1982), but such exclusion would seem to be excessively strict. A large study of the relationship of handedness to CT asymmetries and to family histories of handedness demonstrated that 22% of right-handed men have a left-hander in the family (Koff *et al.*, 1986). It does not seem reasonable to exclude this patient because 1 of 9 first degree relatives was left-handed, although it is important to note the family history as future studies may identify a role for the factor of family history of handedness in crossed aphasia.

Case 2

The subject is a 65-yr-old college-educated woman who speaks only English. She is fully right-handed, and has no family history of left-handedness. There is no past history of neurological events. In June 1987 she had a subarachnoid haemorrhage from a right posterior communicating artery aneurysm. There was acute hydrocephalus which was treated by a shunt operation. The aneurysm was clipped on day 11. For the next 3 days there was fluctuating alertness, unspecified aphasia and a left hemiparesis. Eight days after the clipping and 19 days after the haemorrhage, the patient was noted to be speaking 'gibberish'. She was transferred to Braintree Rehabilitation Hospital where we examined her at 4 and at 9 weeks postonset.

Neurological examination revealed a mild left hemiparesis, greater in the leg than the arm, a very mild left-sided sensory loss, and no visual field defects or neglect. There were no impairments in articulatory agility, speech prosody, including affective elements, or voice volume. There were no neurological abnormalities on the right side of the body.

Language examination

Spontaneous output was fluent, grammatical, but moderately empty with significant phonemic and semantic paraphasias. There was mild pressure of speech.

Auditory comprehension was nearly normal. There was mild confusion for the identification of low frequency body parts (10/12). Pointing span was only 2, but the Token Test score was 35/39 correct. Comprehension of complex yes/no questions and a variety of grammatical structures was entirely normal.

Confrontation naming was impaired. Errors were seen in all word categories. Phonemic paraphasias and perseveration were common.

Repetition was markedly abnormal with abundant phonemic paraphasias, omission of words, paraphrasia and perseveration. The following are 3 consecutive examples of sentence repetition.

Dogs chase cats → 'Jags docs case, no a dog will chase cats'. Cows eat grass → 'Crats eat grass'. The car is in the garage → 'The cow is in garage'. Recitation was equally paraphasic. The patient was able to produce adequate melody in song.

Writing using the preferred right hand showed good orthography and word structure. The patient was perseverative but generally could write to dictation and to naming most common nouns. Attempts to produce written sentences were marked by word finding difficulties and paraphrasing of intended syntax. Reading aloud demonstrated severe phonemic paralexia. Reading comprehension was normal.

Neuropsychological examination

Ideomotor praxis. There was no buccofacial apraxia. Very mild limb apraxia was evident, manifested as mild spatial rotation errors and during the use of body parts in representational tasks such as pretending to brush her hair.

Visuospatial. There were no problems with basic visual perception. The patient was able to match geometric designs (Benton Visual Recognition Test 16/16) and there was no evidence of neglect on line bisection or visual cancellation tasks. Drawings from copy of simple geometric designs were moderately good, however, complex constructions were markedly distorted and segmented. On the Rey Osterrieth Complex Figure she used a part-by-part problem solving approach and was unable to reproduce the overall configuration of the design. On the Block Design subtest of the WAIS-R she broke configuration on design 2 and achieved a subscale score of 6 (age scaled score was 7). She could identify 14/14 map locations. There was pronounced right/left confusion.

Attention. Concentration for testing was normal. There was no excess fatigability and no motor impersistence. The patient had a reduced auditory span with a pointing span of only 2 and a digit span of 3.

Affect. The patient had normal affective prosody. There was full range of affect.

Emotion. Mood seemed generally appropriate, but the patient was often labile. She exhibited extremely disinhibited, intrusive and socially inappropriate behaviours. She made many self-deprecatory comments about failures and was often surprisingly frustrated and emotional about minor errors.

Course

When reevaluated at 9 weeks postonset, the basic profile described above was unchanged. Spontaneous narrative output was less paraphasic, but phonemic substitutions still were detected

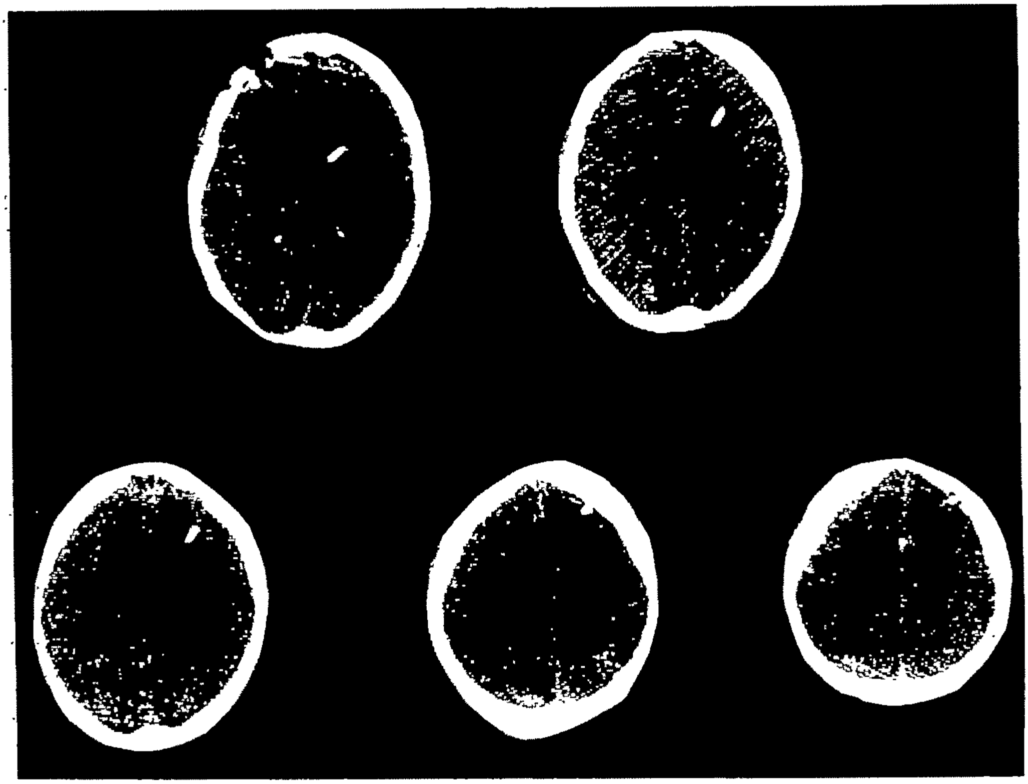

FIG. 2. CT scan of *Case 2* performed 3 weeks after onset. The structures involved by the lesions are discussed in the text.

(quote→'kwait'; garage→'gurrab'). Word finding deficits were mild. Repetition of phonetically complex targets produced abundant phonemic paraphasia with unsuccessful attempts at correction. Digit span was still 3. Writing was much improved although similar letter substitutions were occasionally made. The motor, sensory and visual impairments had completely cleared.

CT findings

An infarct was seen in the right supramarginal gyrus with extension into the posterior superior paraventricular white matter; there was resolving consolidated blood density (fig. 2). There was a second large infarct in the left frontal lobe, predominantly medial and superior. The intraventricular shunt was in the left frontal horn. Right occipital length was greater than that on the left, and left frontal length was greater than that on the right. For right-handed women this is an uncommon pattern of cerebral asymmetries and is considered 'atypical' (Koff *et al.*, 1986).

Summary

In this patient, to infer from the profile of deficits seen after right parietal and left prefrontal lesions, there is also a mixture of anomalous lateralizations of mental function. The patient has impaired spoken and written language, but also mild ideomotor apraxia and significant configuration visuospatial problems.

Many investigators (Joannette *et al.*, 1982) would be reluctant to include this patient because of the complicated neurological course and because of the presence of bilateral lesions. It is even possible that the anomalies in this case are intrahemispheric, i.e., the fluent aphasia is secondary to the left prefrontal lesion. We have included this patient because the aphasia emerged in step with the left hemiparesis and the CT images clearly eliminate any further possible lesions.

LITERATURE REVIEW

Kreindler *et al.* (1966) have suggested that there are several potential profiles of anomalous dominances in both right and left-handers. Their conclusions were based on a review of the literature of crossed aphasia and on an analysis of 5 personally examined cases (2 with tumours and 3 with a vascular aetiology, but none with imaging or postmortem localization). They proposed that language, praxis, and visuospatial function could lateralize independently of each other, and that right and left-handers would have different profiles of anomalous lateralization.

Brown and Hécaen (1976) proposed that in crossed aphasics, as in left-handed aphasics and children with acquired aphasia, analysis of aphasia profiles would reveal an excessive number of cases with nonfluent, agrammatic output regardless of the lesion location. They proposed a unifying theory: all 3 groups had incomplete lateralization which was manifested as agrammatism regardless of lesion profile.

Henderson (1983) described 3 right-handed cases with posterior right hemisphere lesions in whom the aphasia profiles—1 conduction and 2 Wernicke's—were appropriate for the lesion locations had they been in the left hemisphere. He reviewed the existing literature on crossed aphasia and observed that there were very few cases in which both detailed language examination and adequate anatomical information were available. Far from finding an excess of nonfluent cases, he observed that the aphasia profile of crossed aphasia was often fluent and that the lesions in the reported cases were appropriately posterior. He proposed that right hemisphere language representation in crossed aphasics mirrors that of the left hemisphere in routine clinical experience. His hypothesis does not speak to the lateralization of other functions. Two of his cases had a mixture of classical left hemisphere signs (aphasia) and right hemisphere signs (severe constructional impairments and left hemineglect). None of the cases had significant apraxia and none had affective prosody disturbances. Attention, motor impersistence and emotional function were not explicitly reported.

Joanette *et al.* (1982) reviewed all 72 reported cases up to 1981; they determined that only 10 were adequate for analysis, and their analysis was not concerned with exact anatomical correlations. They did note that crossed aphasia could be fluent even in the presence of significant hemiparesis (4 of the 10 cases). They also observed that cases could have primarily subcortical or cortical and subcortical lesions. They noted the coincident occurrence of a classical right hemisphere visuospatial disturbance in 6 cases, and the frequent dissociation between the aphasia profiles of spoken versus written language. They considered possible explanations for crossed aphasia, including incomplete lateralization and mirror image hypotheses, and found evidence to reject them all.

Basso *et al.* (1985*a*) returned to a model similar to that suggested by Kreindler *et al.* (1966). Their results are largely compatible with Henderson's suggestion that the clinical picture which results from right hemisphere lesions is a mirror of that which would have resulted if the lesion had been on the left. There were, however, 2 cases (nos 2 and 5) with anomalous aphasia/apraxia profiles which are incompatible with the theories of Henderson and Brown and Hécaen. Case 2 of Basso *et al.* had neologistic jargon, mildly impaired auditory comprehension, normal repetition except for very lengthy targets, incomprehensible writing, mild buccofacial apraxia, and no significant visuospatial problems. At 4 months postonset, examination was normal. CT demonstrated an infarct in the frontal operculum without striatal involvement. This case is similar to our Case 1, although milder and with better recovery. In the overall group of cases there were frequent dissociations between written and spoken language. The authors suggested that there may be more than one syndrome of crossed aphasia. This report gives explicit consideration to the possibility that crossed aphasics recover more fully than standard aphasics, but they were unable to compare recovery profiles explicitly enough to reach a definite conclusion about whether their cases had recovered more than expected.

We have attempted to review all cases of crossed aphasia after single right hemisphere strokes reported in the past few years in the English or French literature; 34 cases were included for analysis. These were the cases for which detailed language data were presented and that had CT (or at least radionuclide scans) or postmortem studies were available to provide adequate anatomical information. In one report (Pillon *et al.*, 1979), CT scans for the 2 cases were not published, but for their Case 1 the timing of the CT was appropriate and the description sufficiently detailed for inclusion.

For our primary analysis, language data from the postacute epoch (2 weeks to 2 months) were used when available and clearly identified. The aphasia diagnoses that we have affixed in the tables are ours, although most agree with the diagnoses of the original authors. In several cases reviewed below, only language data from the first few days or months postonset were presented or the time postonset of the reported data was not specified. It may be inappropriate to make judgements about behavioural-anatomical correlations in these circumstances so these cases have been indicated in the tables. One report (Hinson *et al.*, 1984) provides adequate detail, but only for an examination done 6 yrs after onset; we have not included this report. Not all 34 cases provided sufficient information to make a diagnosis for every neuropsychological domain.

We have not included analysis of children with crossed aphasia (e.g., Ferro *et al.*, 1982) because of the additional complication of accounting for developmental differences. For a similar reason we have not included cases of congenital lesions even if they first presented in adulthood, such as arteriovenous malformations

(Demeurisse *et al.*, 1986). We have also not included cases of crossed aphasia after brain tumours (e.g., Larrabee *et al.*, 1982; Aboo-Baker and Labauge, 1987; Martins *et al.*, 1987), not because of questions about the laterality of the lesion but because *intra*hemispheric questions are always ambiguous with infiltrative lesions. There are some cases that we did not include because of the absence of a CT scan (or its equivalent) at a time postonset appropriate to define lesion morphology, even if language description was adequate (e.g., Hamasaki *et al.*, 1987).

From our reading of these cases, 22 out of 34 (Table 1) had aphasia profiles which were within plausible expectations of intrahemispheric localization by the standard aphasia correlations (Wechsler, 1976; Urbain *et al.*, 1978; April and Han, 1980; Trojanowski *et al.*, 1980; Carr *et al.*, 1981, Cases 1, 2; Denes and Caviezel, 1981; Yarnell, 1981, Case 1; Brust *et al.*, 1982; Haaland and Miranda, 1982; Henderson, 1983; Kapur and Dunkley, 1984; Sweet *et al.*, 1984; Basso *et al.*, 1985*a*, Cases 1, 3, 4, 7; Mendez and Benson, 1985, Case 3; Rapcsak *et al.*, 1987; Gonzalez Rothi *et al.*, 1987). The problems inherent in defining any 'standard' aphasia correlations are discussed below. In this group the aphasia profile can be considered to show a *mirror image* (Henderson, 1983) of aphasia after left hemisphere injury. This conclusion represents our interpretation of the cases; the authors of some of these reports did not define their cases as we have interpreted them. For example, Urbain *et al.* (1978) described their case as nonfluent and agrammatic, but that conclusion was based on an examination at only 10 days after the stroke. Even then most of the transcribed output seems to be of sentence length and paragrammatical. By 25 days after the stroke, there was prosodic disturbance and phonemic paraphasia, but fluent language structure. The CT lesion was in the posterior portion of Wernicke's area and the supramarginal and angular gyri.

Twelve cases (Table 2) had fluent aphasia (acutely or within a short interval after onset) despite large suprasylvian and prerolandic or perirolandic lesions (Assal *et al.*, 1981; Carr *et al.*, 1981, Case 3; Yarnell, 1981, Cases 2, 3; Assal, 1982; Pillon *et al.*, 1982; Puel *et al.*, 1982; Habib *et al.*, 1983; Basso *et al.*, 1985*a*, Cases 2, 5, 6; Fournet *et al.*, 1987). This is an anomalous group. Eleven of these 12 cases had profound jargon agraphia despite, in some cases, relatively minor spoken language disturbances. These 12 cases can be considered to have an *anomalous* aphasia profile in comparison with aphasia after left hemisphere lesions. The denotations *mirror image* and *anomalous* refer only to the aphasia profile, not to any portion of the other neuropsychological deficits that are discussed below.

We believe that our Case 1 is an example of the anomalous type of crossed aphasia. Despite a frontal and striatal lesion, he had fluent jargon aphasic output. Our Case 2 is probably an example (perhaps a double example) of the mirror image type of crossed aphasia. With a lesion in the *right* supramarginal gyrus, she had a fluent aphasia with primarily phonemic output disturbances, exaggerated in repetition, but normal comprehension.

TABLE 1. MIRROR IMAGE CROSSED APHASICS

	Language		*Apraxia*		
Case	*Spoken*	*Written*	*Facial*	*Limb*	*Summary of published CT*
Wechsler (1976)	Broca	Illiterate	Mild	None	Large suprasylvian, perirolandic (only 1 CT slice published)
Urbain *et al.* (1978)	Conduction	Same	Mild	None	Supramarginal gyrus, angular gyrus, superior temporal gyrus
April and Han (1980)	Broca	Same/ severe	N/A	N/A	Large suprasylvian and frontal opercular
Trojanowski *et al.* (1980)	Broca	Same	N/A	None	Large prerolandic gyrus
Carr *et al.* (1981) 1*	Mild Broca	N/A	N/A	N/A	Frontal opercular (isotope scan)
Carr *et al.* (1981) 2	Probably global	Same	N/A	N/A	Large putaminal haemorrhage
Denes and Caviezel (1981)	Mild Broca to anomic	Same/mild	Mild	None	Frontal cortical and subcortical
Yarnell (1981) 1	Wernicke	Same	N/A	N/A	Superior temporal and supramarginal gyri (isotope scan)
Brust *et al.* (1982)	Akinetic/ echolalic		Too akinetic to test		Large medial frontal incl. supplementary motor area (postmortem)
Haaland and Miranda (1982)	Conduction	Same/mild	N/A	None	Small posterior peri-insular
Henderson (1983) 1	Conduction	Same	None	None	Inferior parietal and caudate-capsular
Henderson (1983) 2	Wernicke	Same	None	Very mild	Posterior temporal and temporoparietal junction
Henderson (1983) 3	Wernicke	Same	None	Very mild	Inferior parietal; extremely large ventricles
Kapur and Dunkley (1984)**	Mild TCMA	Same	None	None	Large capsularputaminal with PVWM (postmortem)
Sweet *et al.* (1984)	Wernicke	Same	N/A	None	Superior temporal and supramarginal gyri (postmortem)
Basso *et al.* (1985*a*) 1	Mild Broca	Severe	None	None	Large frontal opercular and caudate-capsular
Basso *et al.* (1985*a*) 3	Transcortical sensory	N/A	None	Severe	Large medial occipital-temporal and paramedian thalamic
Basso *et al.* 1985*a*) 4	Wernicke to conduction	Same	Mild	None	Superior temporal, supramarginal, angular gyri
Basso *et al.* (1985*a*) 7	Broca to mild Broca	Same	None	None	Large frontal opercular and peri-insular
Mendes and Benson (1985)*	Conduction	Impaired	None	None	Large supramarginal, angular, and superior temporal gyri
Gonzalez Rothi *et al.* (1987)**	Normal	Severe	None	None	Lateral parieto-occipital
Rapcsak *et al.* (1987)	Broca	Same	Severe	Severe	Large suprasylvian, perirolandic and striate-capsular

* Only assessment earlier than 2 weeks. ** Only assessment later than 3 months. N/A = no information available. TCMA = transcortical motor aphasia; PVWM = periventricular white matter.

TABLE 2. ANOMALOUS CROSSED APHASICS

	Aphasia		*Apraxia*		
Case	*Spoken*	*Written*	*Facial*	*Limb*	*Summary of published CT*
Pillon *et al.* (1979)	Mild TCMA	Jargon	None	None	3 cm, subrolandic, pre- and postrolandic
Assal *et al.* (1981)	Conduction	Jargon	Mild	None	Large suprasylvian, perirolandic (postmortem)
Assal (1982)*	Conduction	Jargon	Impaired	None	Large frontal opercular, perirolandic and inferior parietal
Carr *et al.* (1981)	Transcortical sensory	Same/ severe	N/A	N/A	Large deep perirolandic
Yarnell (1981) 2*	Conduction	Same/ severe	Impaired	N/A	Very large suprasylvian, perirolandic
Yarnell (1981) 3	Wernicke	Same/ severe	None	None	Very large perisylvian, perirolandic
Puel *et al.* (1982)	Broca to conduction	Jargon	Mild	None	Very large perisylvian, perirolandic and frontal
Habib *et al.* (1983)	Conduction/ mild	Jargon/ mild	N/A	N/A	Capsular-putaminal with deep frontal PVWM
Basso *et al.* (1985*a*) 2	Transcortical sensory	Jargon	Mild	None	Large frontal opercular
Basso *et al.* (1985*a*) 5	Anomic	Jargon	Impaired	Impaired	Large perisylvian, perirolandic
Basso *et al.* (1985*a*) 6	Wernicke/ mild to normal	Jargon	None	None	Capsular-putaminal haemorrhage
Fournet *et al.* (1987)	Conduction	Jargon	None	None	Large perisylvian, perirolandic and frontal

* Only assessment later than 3 months. TCMA = transcortical motor aphasia. PVWM = periventricular white matter.

Ideomotor apraxia

Eleven of 24 cases (Tables 1, 2; no information in 10 others) showed buccofacial apraxia (Wechlsler, 1976; Urbain *et al.*, 1978; Assal *et al.*, 1981; Denes and Caviezel, 1981; Yarnell, 1981, Case 2; Assal, 1982; Puel *et al.*, 1982; Basso *et al.*, 1985*a*, Cases 2, 4, 5; Rapcsak *et al.*, 1987). Three of 27 (Tables 1, 2; no information in 7 others) showed limb apraxia persistent beyond the acute period (Basso *et al.*, 1985*a*, Cases 3, 5; Rapcsak *et al.*, 1987). Case review indicates that at least 6 others could plausibly have been expected to show significant limb apraxia with the same lesion in the left hemisphere (Wechsler, 1976; Yarnell, 1981, Case 3; Assal, 1982; Puel *et al.*, 1982; Kapur and Dunkley, 1984; Basso *et al.*, 1985*a*, Cases 1, 7; Mendez and Benson, 1985).

Visuospatial impairment

Fourteen of 30 (Table 3; no information in 4 others) had significant left neglect and/or major constructional difficulties of a type that suggested right hemisphere lesions (Pillon *et al.*, 1979; Carr *et al.*, 1981, Cases 1, 3; Haaland and Miranda, 1982; Puel *et al.*, 1982; Henderson, 1983, Cases 2, 3; Kapur and Dunkley, 1984; Sweet *et al.*, 1984; Basso *et al.*, 1985*a*, Cases 3, 7; Mendez and Benson, 1985, Case 3; Fournet *et al.*, 1987; Rapcsak *et al.*, 1987).

Affect and attention

There were scattered examples of inappropriate affect and global attention disorders (Table 4); usually no information was reported. There was no obvious distribution of these deficits with either aphasia group (mirror effect or anomalous). In the 10 cases in which a specific statement was made about affective prosody, there were no abnormalities (Table 4); only 5 of these cases (Pillon *et al.*, 1979; Denes and Caviezel, 1981; Assal, 1982; Puel *et al.*, 1982; Rapcsak *et al.*, 1987) had lesions in either the prerolandic region or the descending motor pathways where impairments in affective prosody might have been expected (Ross, 1981). Specific information about emotional state was generally not provided in these reports.

TABLE 3. HEMIFIELD NEGLECT AND CONSTRUCTIONAL IMPAIRMENTS

Mirror image cases		
	Neglect	*Spatial*
Henderson (1983) 1	None	Mild (L)
Henderson (1983) 2	Severe	Severe (R)
Henderson (1983) 3	Severe	Severe (R)
Brust *et al.* (1982)	Too akinetic to test	
Haaland and Miranda (1982)	None	Moderate (mixed L and R)
Yarnell (1981) 1	N/A	N/A
Denes and Caviezal (1981)	None	Normal
Carr *et al.* (1981) 1	N/A	Severe (acute only)
Carr *et al.* (1981) 2	N/A	Moderate
Urbain *et al.* (1978)	None	Mild (L)
Wechsler (1976)	None	Normal
Sweet *et al.* (1984)	Severe	Severe
Basso *et al.* (1985*a*) 1	None	Mild
Basso *et al.* (1985*a*) 3	Severe	Severe
Basso *et al.* (1985*a*) 4	None	Mild
Basso *et al.* (1985*a*) 7	Severe	Severe
April and Han (1980)	N/A	Impaired
Trojanowski *et al.* (1980)	N/A	N/A
Kapur and Dunkley (1984)	Severe	Severe
Mendes and Benson (1985)	Severe	Impaired
Gonzalez Rothi *et al.* (1987)	None	None
Rapcsak *et al.* (1987)	Moderate	Severe

Anomalous cases		
	Neglect	*Spatial*
Habib *et al.* (1983)	Mild	Mild
Yarnell (1981) 2	Mild	N/A
Yarnell (1981) 3	N/A	N/A
Carr *et al.* (1981) 3	Severe	N/A
Assal (1982)	None	Mild (L)
Assal *et al.* (1981)	Mild	Normal
Pillon *et al.* (1979)	Mild	Impaired
Puel *et al.* (1982)	Severe	Normal
Basso *et al.* (1985*a*) 2	None	None
Basso *et al.* (1985*a*) 5	Mild	Moderate
Basso *et al.* (1985*a*) 6	None	None
Fournet *et al.* (1987)	Severe	Moderate (R)

TABLE 4. CLASSICAL RIGHT HEMISPHERE SIGNS IN CROSSED APHASIA

	Affect				
Case	*Prosody*	*Mood*	*Concern*	*Attention*	*Music*
Henderson (1983) 1	Normal	Normal	Normal	Normal	Normal
Henderson (1983) 2	Normal	Euphoric	Reduced	Normal	Normal
Henderson (1983) 3	Normal	Normal	N/A	Normal	Normal
Denes and Caviezel (1981)	Normal	Normal	Normal	Normal	N/A
Assal (1982)	Normal	Normal	N/A	Normal	N/A
Urbain *et al.* (1978)	Normal	Normal	N/A	N/A	N/A
Puel *et al.* (1982)	Normal	Normal	Normal	Normal	N/A
Pillon *et al.* (1979) 1	Normal	Euphoric	Reduced	Normal	N/A
Fournet *et al.* (1987)	Normal	Normal	Normal	Impaired	N/A
Yarnell (1981) 3	N/A	N/A	N/A	Impaired	N/A
Basso *et al.* (1985*a*) 3	N/A	N/A	N/A	Impaired	N/A
Rapcsak *et al.* (1987)	Normal	Normal	N/A	N/A	N/A

There was also too little systematic information about CT asymmetries to reach any conclusions about a relationship with aphasia type. Henderson *et al.* (1984) have reviewed the CT asymmetries in many of the modern cases. They concluded that there was no relationship between the occurrence of crossed aphasia and the pattern of cerebral asymmetries; the majority of cases available for review seemed to be of the mirror effects variety. Our anomalous case (Case 1) had typical asymmetries and the mirror case (Case 2) had reversed asymmetries. It remains to be demonstrated whether cerebral asymmetries might define a relationship between the type of crossed aphasia and the underlying gross cerebral morphology.

DISCUSSION

Level of analysis of reported cases

In the literature on crossed aphasia, there are at least four different levels of analysis in different reports. First, many reports describe cases from an anecdotal standpoint as virtual curiosity pieces. Further reports of this type do not appear necessary. Secondly, some reports attempt to define the incidence of crossed aphasia; most reports, ours included, are not population studies and cannot inform about incidence. Most authorities seem to accept the 1-2% figure of Gloning *et al.* (1969). Thirdly, a few reports explicitly grapple with the biological or neuropsychological mechanisms of cerebral localization of function as implied by these unusual cases. This level of analysis requires explicit description of the cognitive operations other than language, as well as the subcomponents of language. This is the challenge of Kreindler *et al.* (1966). Basso *et al.* (1985*a*) have an excellent consideration of this problem, as do many of the reports that we designated anomalous. Fourthly, there is a level of analysis that suggests that these cases of radical exception to standard cerebral localization may define the boundaries along which cognitive functions dissociate in the less radically, but still exceptional, atypical left hemisphere lesion cases (Basso *et al.*, 1985*b*). This level of analysis has not been investigated systematically, although its potential importance has been recognized (Caplan, 1987).

Prevalence of anomalous profiles in crossed aphasia

Reconciling the disparate observations and levels of analysis is not entirely possible at present, but some tentative conclusions about crossed aphasia may be advanced. Detailed literature review does support Henderson's (1983) conclusion that there is an overall conformity between the clinicoanatomical relationships of crossed aphasia and classical aphasia. There are two elements to this overall conformity. First, the aphasia profile is 'appropriate' for the intrahemispheric lesion location. Secondly, the components of the aphasic profiles—spoken and written—are congruent with the classical profiles. That there might be an overall conformity of the language disorder says nothing about conformity of any other neuropsychological deficits.

In our review, however, 35% of the reported cases had dramatic language and/or clinicoanatomical anomalies. Among these anomalous crossed aphasia cases there is some overall similarity, but they are certainly not uniformly or even predominantly nonfluent cases as asserted by Brown and Hécaen (1976). They are, in fact, uniformly fluent. Both elements of the overall conformity may be anomalous. First, language profile is anomalous given the intrahemispheric locus of the lesion; obviously, analysis at this level motivated our designation of the cases. All 12 patients had fluent, often paraphasic, language, despite predominantly anterior or deep and anterior lesions. The second factor defining conformity is congruity of the components of the aphasia profile whatever the lesion site. In some cases—our Case 1, Case 2 of Basso *et al.* (1985*a*), and the case of Habib *et al.* (1983), for example—written and spoken language were equally fluent and paraphasic, and comprehension of written and spoken language was similar. But other cases—Case 5 of Basso *et al.* (1985*a*), the case of Fournet *et al.* (1987), perhaps the case of Assal (1982) and also Case 1 of Pillon *et al.* (1979)—had anomalous dissociations between impairments in written and spoken language. These patients are doubly anomalous, both in the intrahemispheric dimension and in the internal relationships of the language components. Perhaps in this subset of anomalous crossed aphasia, the central perirolandic regions of the right hemisphere have a specific but restricted role in language, primarily at a phonemic level. This would account for the several 'unexpected' conduction aphasics whose primary language abnormality was phonemic substitution in spoken and written language. Alternatively, perhaps these cases have an even more discretely restricted impairment at the phoneme-grapheme correspondence level—hence the large number of phonemic jargon agraphics.

Thus far we have only used 'anomalous' to refer to the aphasic profile. The patients had other neuropsychological deficits that potentially might be equally atypical. Praxis, particularly limb praxis, seems frequently to be spared in cases of crossed aphasia. Perhaps, as a general rule, limb praxis is more strongly related to handedness than to spoken language. Thus in these cases limb praxis would segregate with handedness and not aphasia. This could be compatible with case reports of persistent severe limb apraxia accompanied by little (Selnes *et al.*, 1982) or no (Junqué *et al.*, 1986) aphasia after major left hemisphere infarcts in right-handers.

Superimposition of impairments typical of right hemisphere damage has been noted in about one-third of reported cases. These impairments can be either in global or hemifield attention or in visuospatial functions. The presence of 'typical' right hemisphere lesion disturbances has been described both in the mirror and the anomalous aphasic cases. The report of Basso *et al.* (1985*b*) again speaks to the need for a general account for all anomalies. In their report, there were 6 cases with language disorders that were 'exceptions' after left hemisphere lesions with intrahemispheric lesion profiles similar to our Case 1. Detailed information is provided on 2 cases. Case 18 had a score on a test of constructional ability of 0/20; Case 20 had a similar lesion and a similar, but milder, aphasia with a score of 18/20 on the same test. It seems that spatial functions may have their own independent mechanism for anomalous development, but any specific relationship of impaired spatial functions to any or all of the aphasia profiles has not been demonstrated. Likewise, no specific relationship has been suggested between the attentional and emotional disturbances and the aphasia in these cases.

Problems in defining 'exceptions' and anomalous profiles

There are several partly related methodological and theoretical problems that profoundly confound any conclusions, including ours, about anomalies in crossed aphasia. The first problem is the absence of any acceptable metric for what is or is not anomalous for standard aphasia (left hemisphere lesions in right-handers). The label 'anomalous' often simply depends upon the diagnostic system used. Strictly taxonomic systems (Kertesz, 1979) will find a typical label for virtually all cases, with 'anomic aphasia' serving as a safe harbour for otherwise heterogenous cases. There will be no anomalous cases in this taxonomy. Systems based on venerable but clinical notations of the classical syndromes (Goodglass and Kaplan, 1983) may find a typical label for only 40% of cases (Albert *et al.*, 1981). In a recent and very careful analysis (Basso *et al.*, 1985*b*) of a large population of standard aphasics (excluding cases with solely subcortical lesions), only 17% had aphasia profiles that did not conform to the classical syndromes. Among these nonconforming cases, there were numerous different variations from 'anticipated' findings, although 6 of the 36 exceptions were fluent aphasics (a variety of syndrome diagnoses) despite exclusively anterior and suprasylvian lesions. The 12 anomalously fluent crossed aphasia cases reviewed here were, on the contrary, more—although not entirely—homogeneous, and they were 100% of the '*intra*-hemispheric exceptions'.

There is one important limitation to the interpretation of all studies to date of the 'exceptions' to aphasia classification, namely the absence of adequate consideration of the specific contributions of subcortical lesion sites to the clinical profile. Even the otherwise estimable report of Basso *et al.* (1985*b*) gives sparse attention to the subcortical extent of lesions and even that attention does not differentiate reliably between periventricular extent and shallower subcortical involvement. There is ample evidence that specific subcortical lesion profiles have specific correlations with aphasia profiles (Damasio *et al.*, 1982; Alexander *et al.*, 1987; Alexander, 1988). We believe that several of the exceptions in the report of Basso *et al.* (1985*b*) might be less exceptional with consideration of subcortical lesion extent in addition to their focus on cortical lesion site. Is it exceptional to find Broca's aphasia without a lesion in Broca's area if there is a lesion in the entire anterior periventricular white matter (Knopman *et al.*, 1983)? This is not an argument to expand the number of classical syndromes, rather an argument to consider all elements of anatomy before discarding it as an explanatory tool. In our literature review, we attempted to consider all aspects of anatomy. For instance, the case of Assal *et al.* (1981) might be anomalous precisely because of the subcortical lesion extent into deep frontal lesions.

The second problem in interpretation of anomalies is syndrome drift. Not only must a syndrome be specified as 'appropriate' for a given anatomical location, but it also must be specified as 'appropriate' for a given time in the course of the illness. Kertesz and McCabe (1977) considered this issue explicitly, demonstrating a number of common syndrome shifts over time. Mohr (1976) has reflected on this problem for the specific case of Broca's aphasia. The conclusion from Mohr seems inescapable: persistent Broca's aphasia is usually a late-appearing syndrome of partial recovery. Similar conclusions about anomic aphasia as the residual profile of acute Broca's aphasia are reached in the follow-up studies of Kertesz and McCabe (1977). Others have explicitly (Prins *et al.*, 1978; Knopman *et al.*, 1983) or implicitly (Leischner, 1976) demonstrated the same phenomenon.

For purposes of anatomical correlations, Mazzocchi and Vignolo (1979) proposed a set of rules to deal with syndrome shift that we found sensible and attempted to follow. The strongest and most direct correlations were between postacute images (more than 3 weeks postonset) and postacute behaviours (3 weeks to 2 months). Admittedly, the interval designated 'postacute' is arbitrary and may be 2 months, 3 months or more. In some cases, the very late profile may not differ at all from the postacute profile. but study of any epoch other than the postacute should be clearly designated. Perhaps the issue of time postonset is a factor in the report of Basso *et al.* (1985*b*). For instance, 4 of 9 Wernicke's aphasics with anterior lesions were first evaluated at more than 5 months postonset. In our review of the literature on crossed aphasia, we have indicated in the tables any case for whom the available language examination was not from the postacute interval. As described above, when both the acute and postacute intervals were described, we took the postacute even if the original authors relied on the acute.

The third methodological problem is that most studies of crossed aphasia have attempted to classify only into the classical syndromes. Whatever are the merits of classical syndromes as clinical diagnoses in neurology (Benson, 1979), they are certainly too polytypic to serve as the elemental units of disordered language (Caramazza, 1984; Schwartz, 1984). It is a testimony to the clinical validity of the syndrome that 83% of all cases with single lesions might find a home within one of them, but we have argued in other contexts (Alexander, 1988) that it is more profitable to analyse brain behaviour relationships at the level of individual speech or language signs than at the level of the syndrome. Robust biological relationships may be found between specific, perhaps overlapping, distributed anatomical systems and specific speech or language systems. Thus far this argument seems most forcefully made for subcortical structures and their cortical projections (Alexander and Naeser, 1988). For all the cases of crossed aphasia that we reviewed, we attempted this type of sign-by-region analysis when sufficient language detail and lesion image were presented. We do not suppose that the individual clinical signs that we have analysed are the elemental units of language disorder. They are, however, closer than syndromes. Hence, to repeat, the syndrome designations on the tables are to orientate the reader to the general profile of language to facilitate review.

A final problem is the possibility that recovery is more rapid or more complete in crossed aphasics, but there is, as yet, inadequate analysis of enough cases over time to be certain. There are isolated cases in which recovery seems quite exceptional. The patient reported by Denes and Caviezel (1981) could be interpreted as an appropriate postacute syndrome but with exceptionally complete recovery at 6 months. In our Case 2 recovery was prompt, but probably not unexpected for a small haemorrhagic infarct in the supramarginal gyrus. In the very anomalous cases, it is difficult to know how to judge 'expected' recovery.

With all of those caveats about what is 'appropriate' or 'exceptional' or a 'precise fit' or 'standard', can we argue for 'anomalies' at all? The patients are statistically anomalous by being aphasic at all after right hemisphere lesions. With characterization of aphasics at the gross level of the syndrome and with little consideration of subcortical anatomy, only 17% of standard cases cannot be accounted for, and only 6 (examples 15–21, 3% of all cases) of the 'exceptions' of Basso *et al.* (1985*b*) had clinicoanatomical profiles very similar to our anomalous cases, that is, fluent paraphasic aphasias with suprasylvian, primarily perirolandic lesions generally similar to our Case 1. In comparison, 35% of crossed aphasia cases cannot be accounted for even with consideration at the subsyndromic level and with explicit consideration of subcortical anatomy. We believe that this argues for significant anomalies among crossed aphasics. Further, the very problem of defining anomalies emphasizes the importance of searching for an explanation of all 'anomalous' cases whether the lesion is right or left. Crossed aphasics may simply offer greater opportunity to explore this issue than 'standard' aphasics.

Potential general value in the study of crossed aphasics

It is possible that the neurobiological rules (assuming that some exist) which govern the separate lateralizations of separable cerebral functions can be uncovered by asking the same experimental questions of other groups of atypical patients. There are reports of crossed apraxics (Mani and Levine, 1987). There are reports of right-handers with left hemisphere lesions without aphasia but with severe spatial and/or limb praxis disturbances (Heilman *et al.*, 1974; Selnes *et al.*, 1982; Junqué *et al.*, 1986). These patients presumably would have presented with crossed aphasia had they suffered right hemisphere lesions. Perhaps even left-handers with unilateral brain lesions may segregate into similar groups: one group organized precisely as right-handers (Naeser and Borod, 1986), a second group with mirror effects for all cognitive domains, that is, in which the anomalies are only *inter*hemispheric (Taylor and Solomon, 1979; Delis *et al.*, 1983), and a third, and probably smallest group, with anomalous lateralizations and localizations (Heilman *et al.*, 1973; Case 2 of Archibald, 1987).

CONCLUSIONS

It seems then that there are several possible partitions of lateralized functions, although not precisely along the lines suggested by Kreindler *et al.* (1966). There may be several testable hypotheses about the linkage of dissociated functions in crossed aphasics. (1) In some crossed aphasics the phonological and semantic levels of language may be lateralized differently. (2) Limb praxis may be more strongly correlated with handedness than is language. (3) Buccofacial praxis may be more closely correlated with the hemisphere responsible for speaking. (4) The bizarre quality of unspoken output in some cases may be associated with superimposed right hemisphere-like attentional impairments. (5) Affective prosody and melody in song may always lateralize together. There are undoubtedly other possibilities.

Investigation of these questions will require more precision in specifying the level of analysis than has hitherto been common in the study of crossed aphasics. It will require separate delineation of spoken language and written language, at the level of phonology, phonemics, semantics, and syntax, as well as of buccofacial praxis, limb praxis, visuospatial function (also no doubt subdivisible), hemifield attention, global attention, affect (including prosody), and conscious emotional function. Analysis of lesion location will require consideration of subcortical as well as cortical structures. With anatomy and behaviours defined, it will be possible to ask if the specific profiles (sign-by-sign, not at the level of the syndrome) fit those that might be 'expected' after the same lesion in the left hemisphere.

Beyond just crossed aphasia, similar questions can be asked of all cases with single lesions. Are the lateralized cerebral functions in the 'expected' hemisphere? Anomalies here are the most obvious, but perhaps the least interesting. If lateralization is anomalous, what functions have an obligatory lateralization with or across from each other? Within whichever hemisphere the functions are lateralized, is the intrahemispheric locus of function 'expected'? Again, within either hemisphere, what functions have obligatory relationships to each other? Does interhemispheric anomalous lateralization permit more intrahemispheric anomalous localization? Anomalies in intrahemispheric localization are more dramatic when interhemispheric lateralization is normal—the 'exceptions'—but there is, as yet, no evidence that the intrahemispheric anomalies are fundamentally different if they are in the 'expected' hemisphere or not. These are the real challenges of crossed aphasia.

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PROSOPAGNOSIA IN A RIGHT HEMISPHERECTOMIZED PATIENT

by JUSTINE SERGENT *and* JEAN-GUY VILLEMURE

(*From the Montreal Neurological Institute, Montreal, Canada*)

SUMMARY

The first reported case of prosopagnosia in a right hemispherectomized woman, B.M., whose intellectual and cognitive functions were otherwise normal or only slightly impaired, is presented. She was totally unable to identify, and to experience a sense of familiarity with, faces of persons she knew, but she could evoke semantic information about them and retrieve their names from visual contextual cues. She was unaware that she was lacking face-recognition skills and that faces alone could be used to access the identity of individuals. The functional nature of her deficit was investigated through sensory, perceptual, memory, and learning tasks to determine the level at which her prosopagnosic disturbance occurred. She was defective at resolving low spatial-frequency information, but this was insufficient to explain the selectivity of her impairment. She was able to carry out cognitive operations specific to faces as long as facial identity did not have to be ascertained, and she performed as well as control subjects at deriving information about the gender, age, and emotion of faces. She was impaired at matching different views of the same faces, and multidimensional scaling analysis of dissimilarity judgements between faces indicated an inability to combine the component features into a configurational facial representation that would uniquely define each face. In contrast to recently reported cases of prosopagnosia, B.M. showed no sign of covert recognition of known faces in a learning task, and there was no indication that she could, even for a few seconds, store a faithful facial representation. The occurrence of prosopagnosia in this hemispherectomized patient confirms that this deficit can emerge without damage to the left hemisphere, and her unawareness of her deficit, which had remained unnoticed for several years, raises the possibility that other hemispherectomized patients may be prosopagnosic. The pattern of cognitive impairments displayed by B.M. indicates a perceptual basis to her disturbance and is discussed in relation to other cases of prosopagnosia.

INTRODUCTION

Prosopagnosia is a neurologically-based cognitive deficit characterized by loss of the ability to identify known individuals by their faces, in the absence of severe sensory, intellectual, verbal, and mnesic impairments. It is a selective deficit in several respects, as it can occur without marked disturbances in the visual perception and recognition of objects as long as within-class membership does not have to be ascertained, and it can affect one type of facial information, that

Correspondence to: Dr Justine Sergent, Montreal Neurological Institute, 3801 University Street, Montreal, Quebec, H3A 2B4, Canada.

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conveying the identity of an individual, while leaving unimpaired the processing and interpretation of other types of facial information such as that conveying expression of emotion, age, or sex of the individual. Prosopagnosia thus reflects a failure to access memories associated with a perceived face, but it has so far proved difficult to specify the functional nature of the prosopagnosic disturbance and to understand its underlying mechanisms, partly as a result of its relative infrequency and of the diversity of accompanying impairments. Three issues have become the main focus of investigation into prosopagnosia, and they concern (1) the anatomical correlates of the disturbance and the side of the lesion, (2) the specificity of the impairment with respect to facial identity, and (3) the functional levels at which prosopagnosia occurs, and particularly whether the deficit is primarily perceptual or mnesic in nature.

Much empirical evidence already exists regarding these three issues, but there is as yet no consensus with respect to any of them. Although it was initially thought that a right hemisphere lesion was sufficient to produce prosopagnosia (e.g., Hécaen and Angelergues, 1962; Assal, 1969; Whiteley and Warrington, 1977), recent critical reviews and empirical evidence (Meadows, 1974; Damasio *et al.*, 1982) suggest that damage to the medial occipitotemporal area in both hemispheres is required for the occurrence of the deficit. Yet, aware of this suggestion, researchers from three independent groups have recently reported cases of prosopagnosic patients in whom right-sided damage only could be detected on the basis of CT scans (De Renzi, 1986*b*; Landis *et al.*, 1986; Michel *et al.*, 1986). However, as pointed out by Damasio *et al.* (1986), it cannot be a mere coincidence that all patients whose brains had been subjected to postmortem examination were found to have bilateral lesions, and CT scan is not an infallible technique for the detection of brain damage.

Very few cases of pure prosopagnosia have so far been reported (Bruyer *et al.*, 1983; De Renzi, 1986*a*), and it is theoretically impossible to prove the specificity of prosopagnosia as one can never be certain that all functional capacities of the patient have been thoroughly examined. For instance, one patient presented in support of the specificity of the deficit for faces on the basis of laboratory testing was nonetheless described as having difficulty in discriminating playing cards, coins, and cars (Bruyer *et al.*, 1983). While the impairment for faces is generally the most conspicuous, nearly all prosopagnosics also display difficulty in identifying objects of categories characterized by a close similarity among their respective members (e.g., birds, cars, furniture), suggesting that the deficit may not be restricted to faces but may affect any class of objects the members of which bear a great resemblance to one another (Lhermitte and Pillon, 1975; Levine, 1978; Damasio *et al.*, 1982). It is, however, still debated whether the nonspecificity of the deficit for faces reflects anatomical or functional factors (Young, 1987).

The problem of the functional nature of prosopagnosia is probably the most elusive, and the difficulty in arriving at a single explanation of the deficit has led to the suggestion that there may be at least two types of prosopagnosia (Hécaen, 1981). In some patients, the deficit is thought to be primarily perceptual (Lhermitte and Pillon, 1975; Levine, 1978; Davidoff *et al.*, 1986), while in others it may predominantly reflect a memory disturbance (Benton and Van Allen, 1972; Bruyer *et al.*, 1983). This issue has become still more complicated in recent years following reports of covert recognition of faces by prosopagnosics, indexed either by differential physiological responses to familiar and unfamiliar faces (Bauer, 1984; Tranel and Damasio, 1985) or by behavioural evidence of semantic facilitation with familiar as opposed to unfamiliar faces (Bruyer *et al.*, 1983; de Haan *et al.*, 1987) suggesting that failures of overt recognition do not necessarily imply complete loss of relevant facial information or a total disruption of face-processing mechanisms.

This paper presents the case of a right hemispherectomized woman, B.M., who suffered from a dense prosopagnosia. The case is interesting for several reasons. First, it is, to our knowledge, the first report of prosopagnosia following hemispherectomy (Smith, 1969; Damasio *et al.*, 1975), and some characteristics of B.M.'s deficits point to the possibility that she may not be the only case. Secondly, there was no evidence of left hemisphere damage, and her nearly normal levels of intellectual and cognitive functioning suggest that her left hemisphere must have been essentially intact. Thirdly, B.M., unlike most prosopagnosics described in the literature (*but see* Landis *et al.*, 1986), did not complain of her deficit which was noticed accidentally, and she behaved as if she was not aware that faces alone could be used to access the identity of individuals. Fourthly, her hemispherectomy was carried out when she was aged 13 yrs, and her right hemisphere was still partly functional up to this age, which raises the possibility that her deficit emerged because bilateralization of face processing mechanisms had not yet been achieved by this age. These characteristics, along with an extensive investigation of perceptual and memory skills, provide some new information about the prosopagnosic disturbance.

CASE REPORT

B.M. was a 33-yr-old right-handed American woman who underwent right hemispherectomy when aged 13 yrs in 1967. Her birth and psychomotor development up to 5 yrs of age were normal, at which time twitching of the left leg was noted. These involuntary movements became more pronounced and later involved the left upper limb and the left hemiface. She was operated on in 1961 for excision of epileptogenic brain tissue from the right frontoparietal, parasagittal, central and parietal opercular regions. Postoperatively, the jerking ceased completely, but it reappeared in 1964. She then experienced seizures in the left arm and hemiface, and some episodes could last up to one week continuously. She was entirely refractory to medication, and further excision of frontal and parietal tissues was proposed in 1967. However, examination of the exposed right cortex revealed marked gliosis of the entire frontal lobe and part of the temporal lobe, as well as a badly traumatized and scarred parietal lobe, which led the neurosurgeon to undertake a complete right hemispherectomy, sparing the basal ganglia. Pathological examination of the excised tissue indicated extensive neuronal loss and gliosis in the frontal, parietal and occipital lobes. The hippocampus and the uncus were also markedly gliosed, but the posterior part of the temporal lobe appeared normal. Recovery was uneventful and she was well until 1982 when she started experiencing severe bifrontal headaches, staggering, frequent falls, urinary and stool incontinence, with decrease in judgement, abulia, and loss of interest in her surroundings. CT scan revealed dilated left lateral and third ventricles, suggestive of chronic obstructive hydrocephalus. She was operated on in 1985 for placement of a right ventriculoperitoneal shunt. Recovery was slow but steady and she regained her mental state of before 1982. In 1986, she again presented with deterioration similar to that observed in 1982, and she was found to have a malfunctioning shunt which was replaced by a ventriculoatrial shunt in January 1987. Her mental state greatly improved afterwards, at a higher level than she had ever experienced according to her family, and she has been well since then (last examination in November, 1987). Fig. 1 presents CT scans of B.M.'s brain. They show slight enlargement of the lateral ventricle in the remaining hemisphere, but there was no sign of damage in the left hemisphere.

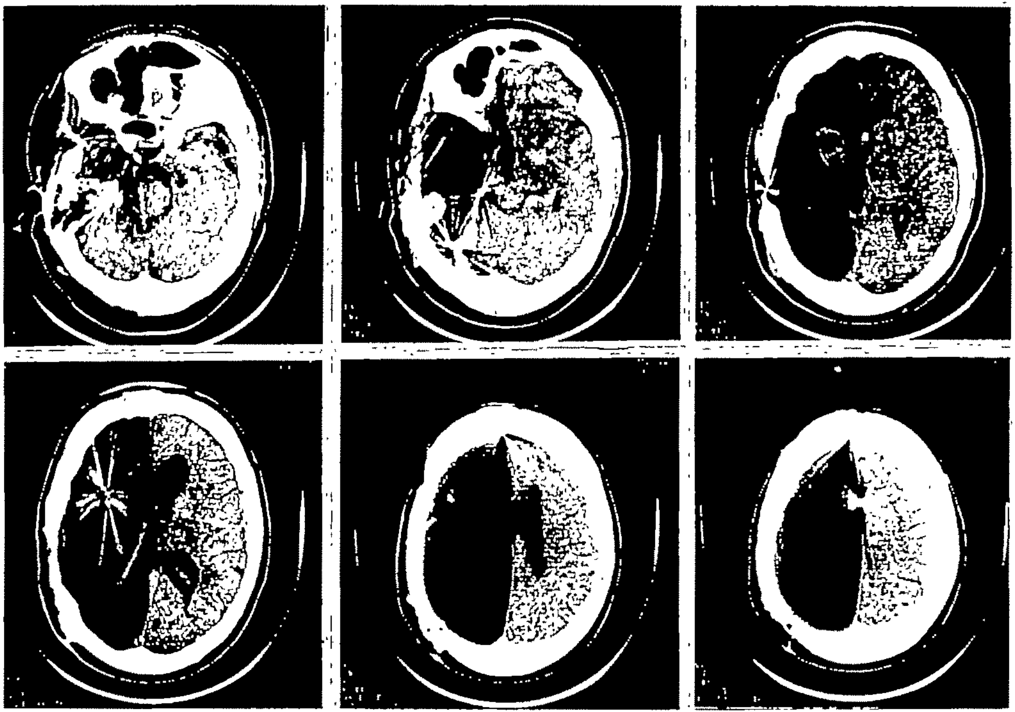

FIG. 1. CT scans of B.M.'s brain (right side of brain on left of figures).

Neurological examination now indicates a dense homonymous left hemianopia, paresis of the upper left limb up to the elbow, atrophy of both left limbs, an extensor plantar response on the left, and decreased sensation over the left half of the body. She walks almost normally.

She is obese, this curtailing much of her social activities. She lives at home with her family and takes care of herself entirely in the house. She has learned to play the organ with the right hand and foot since her hemispherectomy, and she has started to learn to use a word processor.

She did not complain of any impairment, except for paralysis of the left hand and forearm, and of transient difficulty in orientating herself in the hospital. Her deficit in face recognition would have remained unnoticed without a specific event that revealed it. This occurred when the experimenter, still wearing her winter coat, went to see B.M. and told her that she would pick her up in 5 min. When the experimenter, wearing a white coat, came back 5 min later and asked her to come, B.M. replied that she could not because another woman was about to pick her up. This was the only direct evidence of her deficit outside the laboratory but when specifically asked to identify members of the hospital staff taking care of her, she was unable to do so.

When face identification was initially tested in the laboratory (January, 1987), she could not recognize any individual whose name was familiar to her. For instance, she named 5 recent US Presidents, but did not identify any on photographs, even when told that the faces were those of the Presidents she had just named. She was also unable to identify the faces of actors appearing in television programmes she said she was regularly watching. In addition, when presented with faces of 10 American actors and 10 French actors (unknown to her) and asked to tell which ones looked familiar, she said that she had no idea. When requested to guess which were the American actors, she responded at chance level, but she was able to recognize their names and tell the shows or movies in which they appeared.

When asked if she could usually recognize people by their faces, she answered affirmatively; when asked about her responses to the photographs of the US Presidents, however, she said that she was then seeing just their faces and that this was not sufficient to identify the person. She added that she always knows the people she is seeing at home, but that it was more difficult at the hospital because everyone is dressed the same. She did not seem to have realised that faces alone were sufficient to identify people, and she was unaware that she was lacking face-recognition skills. No attempt was made to make her aware of this. It is noteworthy that B.M.'s deficit in face recognition had not been noticed previously in spite of several neurological and neuropsychological examinations. Her mother mentioned that B.M. was sometimes slow at identifying people, but that she had no difficulty at home. She also indicated that she had not noticed any drastic change in this respect since her operation, except during the two recent episodes of confusion resulting from her hydrocephalus, in which cases her whole mental state was affected. Little information was available about B.M.'s capacity to recognize faces before her hemispherectomy, but several facts reported by her mother suggest that she must have had little difficulty in this respect. For instance, her mother recalled that she could identify most of her schoolmates in a group photograph of her class when she was 11, and that she was also able to do so with photographs of relatives taken at a wedding when she was 12. It thus appears that her prosopagnosia is an acquired deficit resulting from the hemispherectomy.

Neuropsychological examination

B.M. had been subjected to neuropsychological testing at each of her visits to the Montreal Neurological Institute and Hospital, both preoperatively and postoperatively. At age 7 yrs, before her first operation, her WISC Full Scale IQ was 95 (Verbal IQ, 91; Performance IQ, 100), and it was not significantly altered by the operation (VIQ 99, PIQ 94). Subsequent preoperative and postoperative testing revealed lower intelligence levels (Full Scale IQ between 70 and 80). This may partly be attributable to her mental deterioration before the operations and because she had not yet fully recovered from the surgery or hydrocephalus at the time of her discharge. There was, however, a marked drop in PIQ after the hemispherectomy (from 94 to 67), indicating that, before surgery, the right hemisphere was still partly functional and contributing to nonverbal cognitive operations despite its structural damage.

She was examined and extensively tested in November 1987, at a time when, in her own words, 'I have never felt better in my life', which was also the opinion of her mother. All the data reported below were collected at that time, and she was then alert, fully cooperative and eager to perform well, capable of sustained concentration, and with an intellectual level in the normal range (VIQ 96, PIQ 91, on the WAIS; *see* Table 1). Most of the tasks to which B.M. was subjected in November 1987 had been tried on her in January 1987, but in a shorter and less systematic form. These tasks were systematized during this interval and tested on control subjects. Thus, unless stated otherwise, B.M.'s performance was compared with that of a group of 50 control subjects, composed of 38 normal adults drawn from an unemployment agency who had participated in laboratory experiments with one of us (J.S.), and of 12 patients in hospital for spinal cord injury (mean age 34.7 yrs; SD 9.12).

B.M.'s speech was fluent but slightly slurred, and her verbal comprehension was normal (60/62 on the Token Test). Writing to copy and dictation, as well as spelling, were unimpaired, and reading was normal, with good comprehension. She was slow at tasks examining constructional ability (Benton *et al.*, 1983) and spatial orientation (maze and route finding), but her performance was within the normal range in terms of accuracy. She had no left hemispatial neglect as examined with the drawing of a clock and the line-crossing test (Albert, 1973), but she showed signs of left extinction when simultaneously touched on both sides of the body. She performed above chance in a reaction time task requiring mirror-image discrimination of rotated alphanumeric characters thought to involve mental rotation (Corballis and Sergent, 1988). By contrast, she was unable to perform an imagery task in which a lower case letter had to be generated from the presentation of the corresponding upper case letter (Sergent, 1989), but she could decide whether or not an upper and a lower case letter presented simultaneously had the same name.

TABLE 1. RAW AND SCALED SCORES ON THE SUBTESTS OF THE WAIS

	Verbal subtests			*Performance subtests*	
	Raw score	*Scaled score*		*Raw score*	*Scaled score*
Information	14	9	Digit symbol	39	7
Comprehension	14	8	Picture completion	17	12
Arithmetic	6	6	Block design	28	9
Similarities	18	12	Picture arrangement	14	6
Digit span	12	11	Object assembly	30	9
Vocabulary	51	11			

Verbal IQ 96. Performance IQ 91.

Overall, her levels of intellectual and cognitive functioning were in most respects within the normal range, and she was able to perform some mental operations, such as mental rotation, thought to be mediated primarily by the right hemisphere (Corballis and Sergent, 1988). Although B.M.'s intellectual capacities were higher than those of most hemispherectomized patients (Goodman and Whitaker, 1985), she is not unique in this respect and some patients have been described with even higher intellectual abilities (e.g., Griffith and Davidson, 1966; Gott, 1973).

Visual perception. Her right visual field was full, she had a dense left homonymous hemianopia with macular splitting, and she displayed no evidence that she experienced 'blindsight' (Weiskrantz, 1986). For instance, when tachistoscopically presented with a bright white light appearing 10° in her left visual field and 5° either above or below the horizontal meridian, she was unable to guess the correct location of the light. In a test of perceptual completion over the anopic field (Sergent, 1988), she showed no sign of completing the missing information and reported seeing no more than was objectively available given her visual field defect. Her visual acuity was 20/20 in the right eye and 20/30 in the left eye. However, her contrast sensitivity, as measured with the Arden (1978) plates (*see* Kobayashi *et al.*, 1985), was impaired in the low spatial frequency range, up to 3 cycles/deg of visual angle, but it was normal in the intermediate and the high spatial frequency range. She could nonetheless detect low spatial frequencies at high contrast. She had no achromatopsia, as determined with the Munsell-Farnsworth 100 hue test and a colour-naming task.

She displayed no visual object agnosia. When tested with the Visually Cued Verbal Cards (Foster *et al.*, 1984) which comprise 295 line drawings of common objects of various categories (people in uniforms, animals, household objects, clothes, food, parts of body), she made only 12 errors due to confusion among objects of close similarity (e.g., dog, wolf, fox; peas and grapes; ring and bracelet). There was practically no category of objects with which she was sufficiently familiar to examine her capacity to make within-class discriminations (such as cars, coins, animals, etc.). The only category was that of green vegetables, and she was presented with 10 colour photographs of such vegetables (Boston salad, Roman salad, broccoli, spinach, cress, parsley, green onion, cucumber, pickle, and zuchini (courgettes)). She could identify only 3 of them correctly when provided with a list of the names which were all familiar to her. When presented with 2 photographs of either 2 different views of the same vegetable or 2 different vegetables and requested to make same/different judgements, for a total of 90 trials, her performance did not significantly differ from chance (51/90; controls: mean 83.32; SD 5.12).

B.M.'s deficit at discriminating between closely similar objects did not extend to the recognition of common objects presented from an unconventional perspective (Warrington and Taylor, 1978). Sixteen objects from the Verbally Cued Visual Cards (Foster *et al.*, 1984) which B.M. had accurately identified when appearing from a canonical viewpoint were selected (cup, plate, fork, toothbrush, sofa, bottle, shoe, pencil, broom, iron, pipe, hat, book, lighter, clothes-peg, reel). She was presented with black-and-white photographs of these 16 objects taken from an unusual angle, and her task was to identify them by name. She provided the correct name for 12 objects, and her 4 errors were in response to objects which were most often misidentified by normal subjects. B.M.'s performance was within the range of normal scores (mean 13.28; SD 1.86), even though there is evidence of a right hemisphere contribution to this perceptual categorization (Warrington and Taylor, 1978; Warrington and James, 1986).

The Wechsler (1945) verbal memory quotient was 91, and her score on the Benton (1974) Visual Retention Test (7/10) was in the low average. On Warrington's (1984) Recognition Memory Test, she obtained scores of 45/50 for words and 28/50 for faces. Her performance with words fell at the 25th percentile of normal sample scores and was below the 1st percentile with faces (Warrington, 1984, Table 5B, p. 7).

B.M.'s performance on the foregoing tests was within the normal range in intellectual and most cognitive functions. Her deficit in low spatial-frequency resolution did not affect her perceptual capacities in reading and object recognition. She was able to derive the structure of common objects presented from an unconventional viewpoint, suggesting that she could achieve appropriate visual representations and perform the transformations and normalizations required to access the stored descriptions of these objects. Her verbal memory was at the low normal range, as was her memory for visual forms, but she performed at chance level in the face recognition test, and the remainder of B.M.'s examination was concerned with her capacities at processing facial information.

INVESTIGATION OF FACE PERCEPTION

A face conveys a large variety of information about an individual, and its physical uniqueness defined by the particular arrangement of specific features constitutes a direct clue to access the identity of the person. A face can also inform about other characteristics of the person, such as gender, age, race, or emotion, and these characteristics can be accessed independent of the identity of the face. The examination of B.M.'s face-processing skills was thus designed to uncover the functional level at which her prosopagnosia occurred, first by investigating her capacity to extract and process facial information unrelated to identity, then by testing her ability to achieve a structured percept of a face and extract the physiognomic invariants characterizing a person.

Facial information unrelated to identity (gender, age, emotion)

B.M. displayed no deficit in processing faces as long as she did not have to take into consideration the individuality of the faces. She had thus no difficulty differentiating male and female faces, even when the hair was hidden. She also performed as well as normal subjects when required to estimate the age of faces. She was presented with 20 faces the age of which ranged between 18 and 65 yrs, and she was requested to rank these faces as a function of their age. She only misplaced 2 faces, and her performance (18/20) was well within the normal range (mean 16.9, SD 2.71). When presented with each of these faces separately and asked to tell their age, she again performed as accurately as normal subjects, allowing for an error of ±3 yrs for each face. This capacity to process facial information independent of face identity was also evidenced by her performance on the Mooney (1960) faces. She was required to tell the gender and approximate age of each of the fragmented faces as quickly as possible. Her performance (4 min 32 s; 37/40 for sex and 34/40 for age) was better than the mean of the control group in both speed (mean 5 min 12 s, SD 53 s) and accuracy (means 36.20 and 34.78, for gender and age, respectively).

She was slightly impaired in the verbal identification of the emotion expressed by a face, using 48 faces from the Ekman and Friesen (1975) series (4 male and 4 female faces with 6 expressions each). She always succeeded in telling whether the emotion was positive or negative. However, she made confusions between fear and surprise (on 6 occasions), and between anger and disgust (on 5 occasions), two pairs of expressions that are visually close to one another and which normal subjects are prone to confuse (B.M.: 33/48; controls: mean 41.56, SD 3.08). Nonetheless, when provided with the names of the 6 basic emotions she had to identify, her performance was within normal limits.

Evidence of a dissociation as a function of the type of facial information to be processed was observed in matching tasks requiring the pairing of 2 faces either in terms of facial expression or of facial identity (using the same 48 faces as earlier). In the expression-matching task, B.M. was presented with 1 target face and 4 different test faces only 1 of which expressed the same emotion as the target face. There were 48 trials and, on half of them, the matching face was of the same sex as the target face and, on the other half, of a different sex. B.M. made 3 errors, which is comparable to the performance of control subjects (mean 46.08, SD 1.24). In the identity-matching task, 1 target face was presented along with 4 test faces expressing different emotions than, but of the same sex as, the target face, only 1 of which was of the same individual as the target. Out of 48 trials, B.M. had 26 correct responses, which is significantly above chance (12), but inferior to the performance of control subjects (mean 45.56, SD 2.01). This finding suggests a deficit in extracting the physiognomic invariants of a face that uniquely convey its identity, and it indicates that this deficit does not extend to the facial information conveying emotion. The subsequent tests examined further the deficit in processing face identity.

Facial information related to identity

To determine the influence of her deficit in resolving low spatial frequencies, B.M. was requested to match faces at different levels of resolution (*see* fig. 2). In this test, the target was always a high-resolution face (such as face A, in fig. 2). Three test faces (1 of which being of the same individual as the target) were presented below the target face, and the task was to point to the face identical to the target. There were 4 categories of faces, and the 3 test faces were always drawn from the same category. The 4 categories are shown in fig. 2, and they were (A) high-resolution faces, (B) low-pass faces, from which intermediate and high spatial frequencies have been filtered out, (C) coarsely quantitized faces, in which the brightness of each square was equal to the averaged brightness of the corresponding area in the original face, and (D) high-pass faces, from which low and intermediate spatial frequencies have been filtered out. There were 8 male and 8 female faces, and the 3 test faces were always of the same gender as the target face.

The results are shown in Table 2. Consistent with her deficit in low spatial-frequency resolution, she performed at chance level when she had to match the target face with either the low-pass (face B) or the coarsely quantitized (face C) faces, and she reported that she could barely see a face in these two types of pictures. By contrast, her performance was well above chance with high-resolution (face A) and with high-pass faces (face D) and, although it was lower than the mean of the control

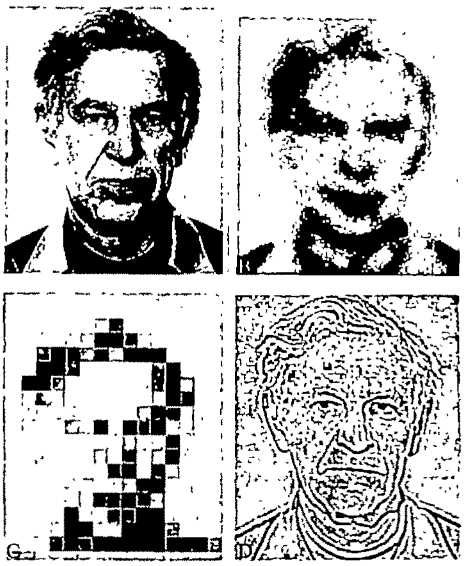

FIG. 2. Sample of the four face versions used for matching: A, high resolution, B, low-pass, C, coarsely quantitized, and D, high-pass.

group, it was no worse than the lowest score of the control subjects. This finding suggests that, even though her deficit in low-frequency resolution influenced her capacity to process low-pass facial information, B.M. had the capacity to rely on high frequency information to achieve an efficient comparison of faces presented from the same point of view (*see* Rizzo *et al.*, 1986), as long as the target and test faces were shown simultaneously.

Her performance on the face recognition test of Benton and Van Allen (1968) was just within the normal range (42/54), but it was achieved at a very slow pace. She was fast and accurate on the first 6 trials (same versions of the target and test faces) but she was much slower on the other trials (different versions of target and test faces). When taking as cut-off point the slowest time for each of the cards by subjects of the control group, her score fell to 14. This was not due to an inherent slowness on the part of the patient, as illustrated earlier by her performance on the Mooney faces, but it seemed to reflect difficulty in extracting the invariant features of faces when different versions of the same faces have to be matched (*see* Newcombe, 1979, for a similar finding).

In another task, she was presented with 20 high resolution front-view faces (such as face A in fig. 2), for 10 s each, and requested to memorize them. She was then immediately presented with these 20 faces mixed with 20 others, and asked to indicate which ones were shown earlier. The results are shown in Table 3. Her performance was no better than chance (11/20) and inferior to the lowest score of the normal subjects (16/20). In a second part, she was presented with the same 20 target front-view faces as done earlier, but the 40 test faces were now 3/4 views, 20 of which were of the

TABLE 2. NO. OF CORRECT RESPONSES IN MATCHING FACES OF DIFFERENT RESOLUTION BY THE CONTROL SUBJECTS AND B.M.

	*Control**	*B.M.*
High resolution	15.96 (16-15)	15
Low-pass	15.24 (16-15)	9
Coarsely quantitized	14.84 (16-12)	6
High-pass	15.70 (16-14)	14

* Mean correct response and range (for 50 subjects).

same individuals as the target faces, and the other 20 were of individuals not shown earlier. Her performance again was not different from chance (9/20) and was inferior to the lowest score of the normal subjects (15/20). About 1 h later, she was again presented with 40 front-view faces, 20 of which were the same target faces and the other 20 were new faces not seen by B.M. earlier. The 1 h interval was filled with 2 sessions of the mental-rotation task mentioned above, with a 20 min break, and she was not presented with faces during this time. Her task was again to indicate which faces were shown earlier. Her results are displayed in the bottom part of Table 3. Although the number of hits was superior to chance (15/20), her performance was in fact no different from chance as she responded equally often to target and nontarget faces.

TABLE 3. NO. OF HITS AND FALSE ALARMS IN IMMEDIATE MATCHING OF FRONT VIEW AND ¾ VIEW FACES AND IN DELAYED MATCHING OF FRONT VIEW FACES

	*Control**		*B.M.*	
	Hit	*False alarms*	*Hit*	*False alarms*
Immediate match Front view	18.80 (20-16)	1.7 (0-3)	11	8
Immediate match ¾ view	17.62 (20-15)	2.3 (0-4)	9	8
Delayed match Front view	16.48 (20-12)	3.7 (0-6)	15	15

* Mean correct response and range (for 50 subjects).

The nature of the operations underlying the perception of faces was examined through a dissimilarity-judgement task with 8 faces that differed on 1, 2, or 3 features, following a procedure already used by Sergent (1984*a*). All 28 possible pairs of different faces were presented to B.M., and her task was to rate the degree of dissimilarity between the 2 faces on a scale of 1 to 9. She performed the task on 4 different occasions, and the dissimilarity judgements were subjected to multidimensional scaling analysis. This analysis served the purpose of uncovering the rules by which the component features of the faces were combined in the comparison, and the data were fitted to two models in order to determine the combination rules. One was the city block model, which best approximates to dissimilarity judgements in which stimuli are compared on the basis of their component features treated additively; the other was the Euclidean model, which provides the best fit for comparison judgements based on the overall configuration of the stimuli, suggesting that the stimuli are treated in terms of their global similarity (*see* Sergent, 1984*a*, for a detailed description). These procedures and analyses have already been applied to a large sample including normal, unilaterally brain damaged, and commissurotomized subjects and, without exception, the Euclidean model has yielded the best fit of the data (J. Sergent, unpublished results). B.M.'s data were analysed with the program KYST-2A (Kruskal *et al.*, 1978) and fitted to city block and Euclidean models for 2 and 3 dimensions. The goodness of fit of each solution was estimated by the 'stress' of the solution, which is a measure of how well the regression fits the dissimilarity judgements: the lower the stress, the better the fit. The MDS analysis showed that the 3-dimensional city block solution resulted in the lowest stress value (0.108), followed by the 2-dimensional city block (0.187), the 3-dimensional Euclidean (0.292) and the 2-dimensional Euclidean (0.331). Such a better fit by the city block model had never been obtained in the many normal and neurological subjects who had performed this task (Sergent, unpublished results), and it indicates that B.M. did not use the configurational properties of the faces in making the comparisons.

It must be noted that the stress value of the best solution was relatively low and of an order comparable to that obtained with normal subjects, suggesting that B.M. had followed the procedure adequately and had performed in a consistent manner. Nonetheless, to examine whether or not the present finding reflected B.M.'s basic perceptual operations, she was tested on two additional sets of stimuli using the same dissimilarity-judgement procedure. These stimuli were 9 coloured patches of constant hue varying along brightness and saturation (Hyman and Well, 1967) and 9 patterns made of convergent oblique lines varying in angle and length (Smith and Baron, 1981), and they were chosen because earlier studies had shown that dissimilarity judgements on these stimuli were best approximated by the Euclidean model (Hyman and Well, 1968; Smith and Baron, 1981; Sergent and Takane, 1987). The same analyses as for the faces were carried out separately for each stimulus set. The obtained stress values were the lowest in the 2-dimensional Euclidean solution for the colour stimuli, and in the 3-dimensional Euclidean solution for the oblique lines. In both cases, the stress values associated with the city block solutions were at least twice as large as those associated with the Euclidean solutions. These results may thus indicate that the unusual finding obtained in the multidimensional scaling analysis of the face stimuli was not due to an inherent incapacity of B.M. to combine several dimensions and treat them in a configurational manner, and that it was specific to the processing of faces.

Familiar persons

During the first examination of B.M., in January 1987, a list of famous persons whose names she knew was established, and photographs of both her and her mother were taken. The faces of these persons were used in the following testing sessions.

When presented with a photograph of her own face among 4 others, she was unable to recognize herself and, when asked to guess, she failed to pick the right one. She did guess correctly on a subsequent occasion, but failed twice on two further presentations. The same outcome prevailed when the face of her mother was presented under similar conditions.

She was again presented with the faces of 5 US Presidents whose names were familiar to her. She did not recognize any of them. When told these were faces of people she knew, she mistook Ronald Reagan for her neurosurgeon, 'because he has dark hair'. Each of these 5 faces were then presented one at a time and, for each face, a correct and an incorrect name were suggested. B.M. was asked to tell which was the correct name, and this was repeated 4 times using different pairings at each trial, for a total of 20 trials. She responded correctly on 11 trials, which does not differ from chance. She never came up with responses better than chance when still photographs of people whose names were familiar to her were presented. This was also the case when the faces of these people were mixed with those of unknown people and she was requested to make familiar/unfamiliar decisions.

To examine whether 'live' faces would result in recognition, 3 of her favourite TV programmes were videotaped and edited, such that two versions of 20 s each were made: in the first, only the face of the person was shown (Bob Parker, Vanna White, Michael Fox) and, in the second, the person was shown surrounded by the decor of the programme ('The Price is Right', 'The Wheel of Fortune', 'Family Ties'). A fourth videotape was made, showing Ronald Reagan's face speaking in the first version, and Ronald Reagan in front of the White House in the second. The first versions were initially shown, without sound, and she failed to recognize any of the faces. The second version was then presented, without sound. She did name 3 of the faces (B. Parker, V. White, R. Reagan), but only after recognizing the context in which they appeared. For instance, she said 'this is "The Price is Right", it must be Bob Parker'; and 'This is in Washington, the White House . . . so it must be the President, that's Ronald Reagan'. Her recognition of the individuals was not based on visual cues from the faces, but was achieved by inference from the context in which the individuals appeared. When she was presented again with the first versions of the videotapes, she failed to recognize any of the faces. However, she did recognize Bob Parker and Vanna White, when the faces appeared together with the sound of their voices, but it could not be determined whether B.M.

recognized the sound of their voices as such or used the content of their speech to infer the name of the presentator.

Attempts at inducing semantic facilitation

An ingenious paradigm designed to examine covert knowledge about faces that prosopagnosics cannot recognize was developed by Bruyer *et al.* (1983). Basically, it involves a paired-associate learning task in which some faces are paired with their correct names and other faces with incorrect names. It has been found that the patients are capable of learning true pairings faster than untrue pairings (Bruyer *et al.*, 1983; de Haan *et al.*, 1987), suggesting that some information about the unrecognized faces could be accessed and thus facilitate the learning of the true pairings. Only one version of this paradigm could be used with B.M., because the relatively small number of famous people she knew would have imposed repetition of the same faces between sessions.

TABLE 4. NO. OF CORRECT RESPONSES PER TRIAL IN THE PAIRED-ASSOCIATE LEARNING TASK WITH TRUE AND UNTRUE PAIRINGS

	Trial no.									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Faces										
True pair	0	0	2	1	1	0	3	0	2	1
Untrue pair	1	0	0	2	1	2	1	2	0	2
Cars										
True pair	1	2	2	3	2	3	3	3	3	3
Untrue pair	2	1	2	2	1	3	3	3	3	3

In this task, 6 faces were presented, each one associated with a name. Three faces were given their true names (Bob Parker, Robert Redford, Richard Nixon), and 3 faces had their names interchanged (Ronald Reagan, Michael Fox, Jimmy Carter). B.M. was given 2 min to learn the face-name associations. Then, at each trial, the faces were displayed in front of her in random order, and each of the 6 names was called out; the task was to point to the corresponding face. There were 10 trials, and the cards were shuffled after each trial so that they appeared in a different order. Errors were corrected at the end of each trial. By contrast with results reported in earlier similar studies (Bruyer *et al.*, 1983; de Haan *et al.*, 1987), B.M. did not show any facilitation in learning the true compared with the untrue pairings (*see* Table 4). Counting the number of correct responses at each trial for true and untrue pairings, there were more correct responses on untrue pairings in 5 trials, on true pairings in 3 trials, and no difference in 2 trials.

In a final attempt at inducing some learning of faces, the 3 photographs used in the true pairing condition were presented one after the other, associated with their true names. This was done 3 times by the experimenter. On the following trials, B.M. was asked to give the name of the corresponding face, and she was corrected when she made an error. She quickly realized that Robert Redford had blond hair, but took 6 trials before achieving correct recognition of the 3 faces on 5 consecutive trials. After a 5 min break, the 6 faces were presented and she was asked to point to the 3 faces shown earlier. She responded at chance, and mistook Jimmy Carter for Robert Redford, 'because of his blond hair'. There was no indication that she had succeeded in storing reliable representations of the 3 faces.

To examine whether B.M.'s performance on the preceding paired-associate learning task reflected simply a failure to display covert face recognition as such or a more general memory impairment, she was tested on the same task with black-and-white photographs of ¾ view of American cars. She was unable to identify any of the cars that were presented, and mentioned that she had no interest in cars, but that she was familiar with the names of cars. In this task, 3 cars were given their correct company names (Chevrolet, Ford, Chrysler) and 3 cars had their names interchanged (Mercury, Buick, Pontiac). Using 10 trials as with faces, she succeeded in learning the car-name associations by the sixth trial (*see* Table 4), suggesting that her earlier failure to learn the face-name associations could not be attributed to an inherent incapacity to achieve paired-associate learning.

DISCUSSION

The pattern of results displayed by B.M. in this study indicates a complete inability to identify familiar people through inspection of their faces, in the absence of major impairments in most other cognitive functions. Her symptoms thus fit well the definition of prosopagnosia, even though two aspects of her deficits depart from the usual pattern of the prosopagnosic disturbance, namely her hemispherectomy and her unawareness of her impairment. These two characteristics will be discussed first; thereafter, the implications of the present findings will be addressed with respect to the main issues related to the study of prosopagnosia.

Characteristics unique to B.M.

The present case is the first report of prosopagnosia in a hemispherectomized patient, and this raises several questions regarding the anatomical correlates of the disturbance and the reasons why B.M. appears to be an atypical case. There are no unequivocal and straightforward answers to these questions, and several factors seem to contribute interactively to the emergence of B.M.'s deficit.

Anatomical correlates. The radiological information available suggests that B.M.'s left hemisphere was essentially normal except for an enlarged lateral ventricle, which is the rule in hemispherectomized patients (Wilson, 1970). As noted earlier, CT imaging is not an infallible technique for detection of brain damage, and it is possible that a lesion in her left hemisphere remained unnoticed. However, indirect support for the intactness of B.M.'s left hemisphere may come from her full right visual field, her nearly normal intellectual levels, the absence of verbal deficits, and from the large variety of cognitive functions of which she was capable with only one hemisphere. Even if we still have little understanding of how the brain organizes its functions, it seems that more impairments would have been expected had part of her left hemisphere been damaged. This cannot be ascertained with certainty but, for the remainder of this discussion, it will be assumed that her left hemisphere was intact. The present finding would thus add to the existing evidence that prosopagnosia may occur as a result of right hemisphere damage along (*see* De Renzi, 1986*b*). However, the relevance of this finding for the general issue of the anatomical correlates of prosopagnosia may be limited as B.M. seems to be an exception among hemispherectomized patients. What has to be explained, then, is why B.M. was prosopagnosic.

Causes of B.M.'s prosopagnosia. Compared with most cases of hemispherectomy (Goodman and Whitaker, 1985; Smith, 1969), B.M. did not suffer from infantile hemiplegia, and her first symptoms appeared only when she was 5 yrs old. Even at the time of her hemispherectomy at 13, her right hemisphere was still partly functional, as suggested by the marked drop in PIQ after the operation and by the pathological examination of the ablated tissue which indicated no apparent damage in the posterior temporal lobe. Thus in contrast to most other hemispherectomized patients whose diseased hemisphere was unfunctional at birth and was removed in the early years of life (Wilson, 1970; Goodman and Whitaker, 1985), B.M.'s brain may have developed normally during infancy and damage in her right hemisphere was initially restricted to the frontoparietal area subserving sensorimotor functions without affecting cortical regions involved in higher-order cognitive processing. It is thus possible that, before her hemispherectomy, the right hemisphere was subserving normal visual perceptual functions, and her PIQ was indeed within the normal range. The right hemispherectomy may then have stripped B.M.'s brain of structures that were mediating face-recognition functions, at a time when the remaining hemisphere had lost much of its functional plasticity and was no longer able to organize itself to take over operations which had so far been mediated by the other hemisphere.

These considerations are not sufficient, however, to explain B.M.'s prosopagnosia. For one thing, not all hemispherectomized patients had their operation during infancy. For another, it is generally agreed that both hemispheres can subserve face recognition, albeit not equally efficiently (Levy *et al.*, 1972; Sergent, 1984*a*). Indeed, the usual absence of prosopagnosia in hemispherectomized patients has been taken as evidence of a contribution of both hemispheres to face recognition (Damasio, 1985). The cause of B.M.'s prosopagnosia must be speculative, but three points may be worth discussing in this respect. First, the idea that both hemispheres are involved in the processing of faces is based on studies of *adult* subjects and may not necessarily apply to subjects whose brain has not yet reached its mature stage. Although this is still a controversial issue, there is not one instance of left hemisphere involvement in face recognition by children (e.g., Young and Ellis, 1976; Young and Bion, 1980; *see* Levine, 1985, for a review), whereas laterality studies in adults abound in evidence of such involvement (e.g., Sergent, 1984*a*). This could indicate that bilateralization of face processing mechanisms develops with time from a dominant right hemisphere contribution to bilateral involvement. Secondly, in support of this suggestion, there is evidence that, in early adolescence, face recognition efficiency is somehow reduced, as suggested by a dip in the function relating recognition accuracy and age (Carey, 1981). This has been attributed to a reorganization of face processing mechanisms resulting from the developing involvement of the left hemisphere in these processes. It may thus be that B.M.'s hemispherectomy took place at a time when such a bilateralization was in the process of occurring and had not yet been completed, and the ablation of the right hemisphere may have made her left hemisphere unable to develop appropriate face processing skills. There is, however, a third point that may have further contributed to B.M.'s prosopagnosia, concerned with the limited need for B.M. to develop refined skills at identifying faces. She has been essentially confined to her home, living with her parents and meeting very few people apart from her close family. In such a context, her unimpaired ability to make male/female categorization and age estimation may have proved sufficient to achieve a discrimination among the few faces with which she was confronted. In as much as the brain develops its processing competence as a function of the individual's needs, there may have been no need for more refined skills at processing faces than those already mediated by her left hemisphere.

This speculative interpretation would suggest that B.M.'s prosopagnosia may have resulted from a combination of factors that converged toward making refined face recognition skills not only difficult to achieve as a result of her right hemispherectomy but also of limited importance given her restricted social life. Had the hemispherectomy taken place sooner, her left hemisphere may have been endowed with more functional plasticity, as typically occurs with early hemispherectomy (Wilson, 1970; Goodman and Whitaker, 1985). On the other hand, had the hemispherectomy taken place later (e.g., Damasio *et al.*, 1975), bilateralization of face processing mechanisms may have then been completed, and the left hemisphere would have been able to mediate face recognition.

B.M.'s unawareness of her deficit. By contrast with most prosopagnosics described in the literature, B.M. was not aware that she was lacking a basic cognitive function. Such an unawareness has been reported by Landis *et al.* (1986) in the few weeks following onset of the illness, but it is not typically observed in patients with long-standing prosopagnosia. B.M.'s unawareness does not seem to reflect a form of anosognosia resulting from her right hemispherectomy. She was quite aware of the paralysis of her left forearm, she had no hemispatial neglect, and she complained about her difficulty in orientating herself in the hospital. Although anosognosia need not affect all deficits resulting from right hemisphere damage and can be selective (Bisiach *et al.*, 1986), B.M.'s unawareness of her impairment is more likely to reflect the fact that her capacity to discriminate between faces was sufficient for her needs. She mentioned, and her mother confirmed, that she had little difficulty recognizing people at home, and this must have been achieved through characteristics such as gender, age, along with clothing, within a given context in which she was exposed to few faces of well-known people. Otherwise, as shown with the 'live' faces, she relied on the context to infer the name of the people she was seeing and, if she could not identify the person and find the name, she just thought that this was not possible.

B.M.'s absence of complaint about her deficit raises the possibility that such an unawareness is characteristic of other patients, which would imply that she may not be the only hemispherectomized patient to be prosopagnosic. Two points may support this suggestion. One is that B.M. had been examined by neuropsychologists on several occasions and yet her deficit had not been noticed; without a specific event that revealed it, her prosopagnosia would not have been detected. A second point is that, except for one case who underwent hemispherectomy at the age of 20 yrs and was not prosopagnosic (Damasio *et al.*, 1975), neuropsychological examination of hemispherectomized patients has not specifically included tests of familiar face recognition. There is, therefore, no strong empirical basis to suggest that hemispherectomized patients are, as a rule, not prosopagnosics. If an absence of deficit was inferred from an absence of complaint, the present case indicates that this may be insufficient and that other cases of prosopagnosia in hemispherectomized patients may exist.

Functional nature of B.M.'s prosopagnosia

B.M.'s prosopagnosia took place in the context of preserved capacity to access the identity of persons, to memorize their names and to evoke information about their professional life and achievement. She was also capable of carrying out operations specific to the processing of faces, such as gender categorization, age estimation, and identification of emotion expressed by a face. She had no object agnosia and was able to recognize objects presented from an unconventional perspective. Except for her difficulty in discriminating between green vegetables and between some objects that looked alike, she was essentially free of perceptual deficits as long as she was not dealing with facial identity.

This pattern of results seems to rule out a significant influence of her deficit in low spatial-frequency resolution on her face recognition ability. This sensory deficit after right hemisphere damage confirms earlier findings in neurological patients (Sergent, 1984*b*; Kobayashi *et al.*, 1985), but it cannot directly explain why it would affect the processing of faces and not that of other objects presented under similar viewing conditions. In addition, although a low-frequency resolution deficit has been observed in other prosopagnosics (Davidoff *et al.*, 1986), it does not seem to be necessary for the occurrence of prosopagnosia (Rizzo *et al.*, 1986; de Haan *et al.*, 1987). However, this does not mean that efficient processing of low frequencies is not required in face recognition, and adequate detection is no guarantee that the detected information is efficiently used at further stages of processing by a damaged brain. There is evidence that memory representations of faces are stored as a function of their low-frequency components (Harvey, 1986), and right hemisphere damage, by impairing operations on low-frequency information (Sergent, 1984*b*), may be detrimental to the processing of faces.

B.M. was impaired at all tasks involving the processing of facial identity, except when she had to match the same views of faces in their high-resolution and their high-pass versions. She was deficient at matching different views of the same faces, whether the difference was at the level of face orientation or illumination (Benton and Van Allen's, 1968, faces), of facial expression (Ekman and Friesen's, 1975, faces), or of face viewpoint (front view compared to 3/4 view). This suggests that B.M. was unable to extract the physiognomic invariants that uniquely define a face, and this suggestion is supported by the results of the multidimensional scaling analysis which indicated an inability to combine the component features into a facial configuration. This seems to be the essential deficit of B.M. who found herself unable to extract the relevant information and to form an integrated representation of faces that would have been necessary for efficient storage and retrieval.

Even though B.M. was defective at all face recognition tasks involving a memory component, this seems to be secondary to her perceptual impairment. She was not capable of storing, even for a few seconds, a facial representation that could be recognized or associated with its name, whether the faces were familiar or unfamiliar, and even when the same views of the faces were presented for recognition in the immediate matching task. This contrasts with her normal score on the digit span of the WAIS (*see* Table 1) and on Warrington's (1984) Word Recognition Test. In addition, even if her repertoire of known people was small, she could access their names from visual contextual cues, and she could provide semantic information about these persons. It was the access to this information from inspection of the persons' faces that was defective in B.M., and this resulted from a failure to form an integrated representation of a person's face because of an absence of appropriate mechanisms to extract the relevant facial information.

The present results, therefore, strongly suggest that the functional nature of B.M.'s prosopagnosia is at a perceptual level. However, it cannot be established whether this applies to all cases of prosopagnosia, as few cases have been subjected to a thorough examination of their perceptual capacities. When such an examination was carried out (e.g., Lhermitte and Pillon, 1975; Whiteley and Warrington, 1977; Levine, 1978; Davidoff *et al.*, 1986; present case), a perceptual deficit appeared to be sufficient to explain the prosopagnosic disturbance, even when the patient displayed a strong impairment in memory for faces. This is not to say that prosopagnosia cannot occur at a memory level, but this can be established only after excluding any perceptual deficit.

Covert recognition of faces

Recent findings that prosopagnosics display covert recognition of faces have provided a new perspective on the prosopagnosic disturbance. Covert recognition has been indexed either by different psychophysiological responses to familiar and unfamiliar faces (through electrodermal skin conductance measures, Bauer, 1984, 1986; Tranel and Damasio, 1985) or by semantic facilitation with familiar as opposed to unfamiliar faces in paired associate learning tasks (Bruyer *et al.*, 1983; de Haan *et al.*, 1987; Sergent and Poncet, 1988). While these physiological and behavioural findings both suggest that face recognition mechanisms are not totally disrupted in these patients who are, in fact, only unaware that recognition has taken place, it has not yet been determined whether a positive finding on each of these two measures reflects similar underlying mechanisms and taps the same functional level of processing.

When B.M. was subjected to the paired-associate learning task, she showed no sign of covert recognition as she did not learn true pairings of a face and a name better than false pairings. On the other hand, her successful performance on the paired-associate learning task with pictures of cars suggests that memory impairment cannot account for her inability to achieve the face-name pairings. Although the present negative finding concerns only one patient, it may offer some indications about the conditions for the occurrence of behavioural covert recognition of faces in prosopagnosic patients and the functional level at which it takes place. An examination of the neurological status of the 3 patients for whom there is behavioural evidence of covert recognition suggests some characteristics unlike those typically encountered in most prosopagnosics. For instance, while Meadows (1974) indicated that more than 90% of prosopagnosics had visual field defects, none of these patients had. In addition, even though the mesial occipitotemporal area is usually found to be the critical site of damage, especially in the right hemisphere (Meadows, 1974; Damasio *et al.*, 1982; De Renzi, 1986*a*; Landis *et al.*, 1986) this area did not seem to be affected in any of these patients. One patient suffered closed head injury and no evidence of intracranial damage or haematoma could be detected radiologically (de Haan *et al.*, 1987); another had right parieto-occipital and left occipital infarcts (Bruyer *et al.*, 1983); and the third had a right temporal lesion of unknown origin (Sergent and Poncet, 1988). It thus appears that *behavioural* evidence of covert face recognition has so far been obtained in patients that do not share some basic features with most prosopagnosics and, although B.M. is herself atypical in some respects, her absence of covert recognition may nonetheless be representative of a perceptually-based prosopagnosic disturbance. It is noteworthy that *physiological* evidence of covert face recognition also comes from patients whose mesial occipitotemporal cortex was spared at least in one hemisphere (Tranel and Damasio, 1985; Bauer, 1986) while the only negative physiological finding reported so far was obtained in a patient with a lesion of the mesial posterior cortex and a severe visual apperceptive agnosia (Bauer, 1986).

Existing evidence therefore tends to suggest that, for covert recognition to occur, perceptual mechanisms for the encoding and differentiation of faces must be essentially intact. It is thus a disturbance in the activation of the stored semantic information about a perceived face that must be responsible for the prosopagnosia in patients displaying covert face recognition as assessed behaviourally or physiologically, although it remains to be determined whether covert recognition can be dissociated depending on the measure used to index it. Whether a prosopagnosic patient is capable of covert face recognition may therefore reflect the functional level at which the disturbance occurs, and the two paradigms now available may provide additional means of identifying and further understanding the nature of the deficit in prosopagnosic patients.

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PARKINSONIAN DEFICITS IN SERIAL MULTIARTICULATE MOVEMENTS FOR SPEECH

by NADINE P. CONNOR,[1, 2] JAMES H. ABBS,[1, 2, 3] KELLY J. COLE[1] *and* VINCENT L. GRACCO[1]

(*From the* [1]*Speech and Motor Control Laboratories, Waisman Center,* [2]*Department of Neurophysiology, and the* [3]*Department of Neurology, University of Wisconsin, Madison, Wisconsin, USA*)

SUMMARY

Unlike the single joint arm movements so commonly the focus of Parkinson's disease (PD) studies, orofacial movements for speech are well-learned, complex motor sequences generated without visual guidance. The present study of upper lip, lower lip, and jaw movements during speech in PD was thus aimed at determining whether (1) PD speech kinematic deficits are comparable to those often observed in simpler limb movements; (2) coordination for multimovement actions such as speech is aberrant in PD, as recently claimed; and (3) the component muscle groups involved in this behaviour manifest uniform deficits. Results indicated that despite reduced amplitudes of jaw and upper lip displacement in PD subjects, all three of these oral movements were of normal duration. Secondly, PD lower lip movements manifested no deficits and bradykinesia (reduced velocity) was only found in movements of the jaw. Finally, there was an indication of movement coordination aberrations in these parkinsonian subjects. Overall, these results not only suggest a difference between orofacial and limb movement impairments in PD, but also document the need to broaden our perspectives on this movement disorder by examining a wider range of functional motor tasks.

INTRODUCTION

The long-standing clinical observations of bradykinesia and hypokinesia in patients with Parkinson's disease (PD) have been supported by kinematic studies of novel, visually-guided single joint movements. There are certain limitations to analyses confined to such simple actions. While PD movement deficits are primarily manifested by reduced velocity and prolonged duration, these appear more pronounced for sequential multijoint actions (Draper and Johns, 1964; Hallett and Khoshbin, 1980; Evarts *et al.*, 1981; Baroni *et al.*, 1984; Accornero *et al.*, 1985; Sanes, 1985; *cf.* Marsden, 1984, 1985; Benecke *et al.*, 1986, 1987). Previous work also has suggested that PD learning difficulties may yield apparent deficits in novel movements that are not manifested in well-learned actions (Frith *et al.*, 1986; Benecke *et al.*, 1987). Finally, it has been demonstrated that PD subjects

Correspondence to: Dr James H. Abbs, Speech and Motor Control Laboratories, Waisman Center, 1500 Highland Avenue, University of Wisconsin, Madison, WI 53705, USA.

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use visual information for movement guidance differently from normal subjects (Flowers, 1978; *cf.* Marsden, 1985; Schneider *et al.*, 1987; Viallet *et al.*, 1987). These considerations suggest that it may not be optimal to characterize PD movement impairments based solely on isolated single-joint actions performed under visual guidance. Examining very simple tasks in PD studies also may mask other serious deficits. For example, recently described PD disturbances in motor coordination (*cf.* Sanes and Evarts, 1985) may be difficult to discern in isolated single joint movements. Likewise, claims that muscle groups consistently manifest different degrees of impairment (Abbs *et al.*, 1987) cannot be addressed if only one muscle group or movement is examined.

To obtain a functional perspective on PD motor deficits it would obviously be worthwhile to evaluate a variety of movement tasks. Motor actions that do not require artificially generated visual targets and involve sequences of well-learned multiarticulate movements need further study. The present study of PD was thus aimed at kinematic deficits in sequential multiarticulate movements for speech to determine whether (1) speech movement deficits in PD are comparable to those reported previously in single joint limb studies; (2) there are coordination deficits or (3) kinematic manifestations of nonuniform muscle group impairments in this population.

METHODS

Subjects

Nine male subjects with idiopathic PD (age range 58–75 yrs, mean 66; years postonset: range 1–23 yrs) and 9 male normal controls (age range 58–71 yrs, mean 63) were selected for study. Informed consent was obtained from all subjects. The PD subjects were all rated as stage 2 or 3 by the same neurologist (Hoehn and Yahr, 1967); a speech pathologist's clinical ratings indicated dysarthria ranging from mild to moderate levels. All PD subjects (with the exception of PD Case 4, who did not follow instructions) were tested in the afternoon within 1 h of taking appropriate levels of dopaminergic enhancement medication and did not exhibit excessive tremor at time of testing. Data obtained from PD Case 4 did not show significant differences from other PD subjects in the measures reported. All control subjects had normal neurological and speech evaluations. In addition, all PD and normal subjects passed a hearing screening test at 35 dB HL in both ears and scored at least 80% on the Mini-mental State examination (Folstein *et al.*, 1975).

Experimental procedures

Subjects' speech movements were recorded during generation of the word 'sapapple'. Oral closure for the first /p/ in this motor task has been studied extensively in young normal subjects (Gracco and Abbs, 1986; Caruso *et al.*, 1988). In addition, stop-plosive consonants such as this were among the most frequently disturbed in a phonemic analysis of PD speech (Logemann *et al.*, 1978).

For each repetition of the speech motor task, subjects were cued by a tone. At least 25 intelligible repetitions of 'sapapple' were obtained from each subject. To transduce orofacial movements contributing to oral closure for /p/, strain-gauges bonded to ultra-lightweight cantilever beams were attached midsagittally on the vermilion border of the upper lip (UL) and lower lip (LL) (Barlow *et al.*, 1983). A jaw (J) transducer of similar design was attached at a location under the chin with placement that minimized skin movement artefact. Using a laboratory computer, inferior-superior UL, LL, and J movement signals were sampled at 500 sps (12 bit resolution) and digitally low-pass filtered with zero phase lag using a Butterworth filter implementation (fourth order, 20 Hz cut-off). Additionally, J signals were subtracted digitally from the LL signals, yielding J and LL signals that reflected their independent muscle actions. Instantaneous velocities were derived digitally from each movement signal.

The three signals (UL, LL, and J) were marked at movement onset and completion (oral closure) for the first /p/ in 'sapapple'; these two events were defined as 10% of the peak velocity associated with acceleration and deceleration, respectively. Using these marks, available computer algorithms provided the following measures for each movement signal (1) movement duration, from movement onset to movement completion; (2) movement displacement magnitude; (3) peak velocity magnitude; and (4) time of peak velocity, relative to a common time reference. This latter measure allowed determination of the sequencing of peak velocities among the multiple movements, a metric previously used to evaluate orofacial movement coordination (Gracco and Abbs, 1986; Caruso *et al.*, 1988). UL, LL, and J movements with displacements less than 1 mm were excluded from analysis. This exclusion of data was not arbitrary, but rather it was an attempt to minimize spurious error associated with the transduction of very small movements, especially those of the UL. As such, this criterion reduced the likelihood of incorporating passive displacements in the kinematic analyses. Small amplitude UL movements also manifested jerkiness in both PD and normal subjects, often yielding several velocity peaks. This jerkiness restricted certain analyses that relied on stereotypic single peak velocity profiles. Similar data elimination procedures have been employed previously (Zimmermann, 1980). All LL and J displacements reached criterion; however, 10.2% of UL measures were eliminated, including all UL measures from PD Case 7.

RESULTS

Kinematics of speech movements

Exemplary patterns of UL, LL, and J movements for PD and normal subjects are shown in fig. 1. It is apparent from these displacement (1A) and velocity (1B) records that the PD subject manifested reductions in J movements; in contrast, LL movements appeared very similar for the normal and PD subjects. These patterns of normal and PD movement differences were supported by quantitative analyses. Duration, peak velocity, and displacement for UL, LL, and J movements are summarized graphically for both subject groups in fig. 2. Two-way analyses of variance were performed on log transformed data for each measure on UL, LL, and J movements to evaluate PD vs normal differences. A significant main effect for group (PD vs normal) in the absence of significant interaction was found for analyses of displacement and peak velocity ($P \leqslant 0.025$). Post hoc t tests indicated that UL and J movements for the PD subjects had significantly smaller displacements than normal ($P \leqslant 0.05$). However, bradykinesia (reduced velocity) was only manifest in PD jaw movements ($t = 3.02$, $P < 0.01$). Moreover, LL movements in PD were not significantly different from normal in duration, peak velocity, or displacement. Finally, none of the PD movement durations was significantly different from normal. Obviously the functioning of all orofacial muscle groups in these PD subjects was not uniform. Also, the elongated movement durations observed so commonly in the limbs were not manifest for any of these movements.

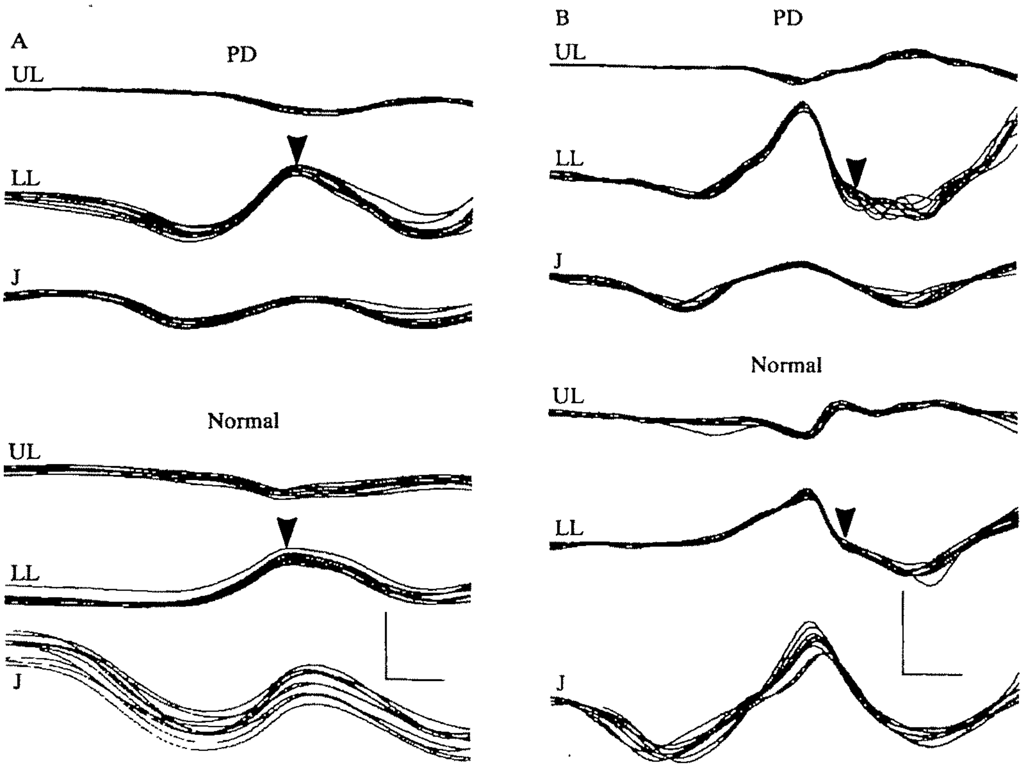

FIG. 1. A, displacements of upper lip (UL), lower lip (LL) and jaw (J) for (*upper panel*) 10 parkinsonian (PD Case 3) and (*lower panel*) 10 normal (Subject 7) records. The completion of oral closure for the first /p/ in 'sapapple' is marked with an arrow. These records demonstrate the consistent trend of relatively normal LL displacements in the PD data, whereas UL and J displacements are reduced relative to normal. The PD subject shown here in fact manifested larger LL displacements than the normal subject. This is not representative of the group data, as indicated in fig. 2. Horizontal and vertical calibration bars represent 50 ms and 10 mm, respectively. B, peak velocities of upper lip (UL), lower lip (LL), and jaw (J) for (*upper panel*) 10 records from parkinsonian (PD Case 3) and (*lower panel*) normal (Subject 7) subjects. The completion of oral closure for the first /p/ in 'sapapple' is indicated by the arrow. In the PD subject, normal LL and UL peak velocities are seen, whereas J peak volocity is reduced. Horizontal and vertical calibration bars represent 50 ms and 200 mm · s^{-1}, respectively.

Differential structure function

To evaluate more directly the uniformity of function of UL, LL, and J muscle groups in these PD subjects, displacement and peak velocity data were transformed to reflect percentage difference from normal levels. Duration data were not included in this analysis, since prior group comparisons revealed normal movement durations across muscle groups for the PD subjects. For the displacement and peak velocity measures, the PD value for each movement was quantified in relation to the overall normal mean (e.g., [(PD value-Normal Group Mean)/Normal Group Mean] · 100). As such, large positive or negative percentages represented a greater difference from normal. Percentage values for the UL, LL, and J were then log-transformed to normalize distributions and then compared with an ANOVA, blocking on subject. Significant F ratios ($P < 0.025$) were found for

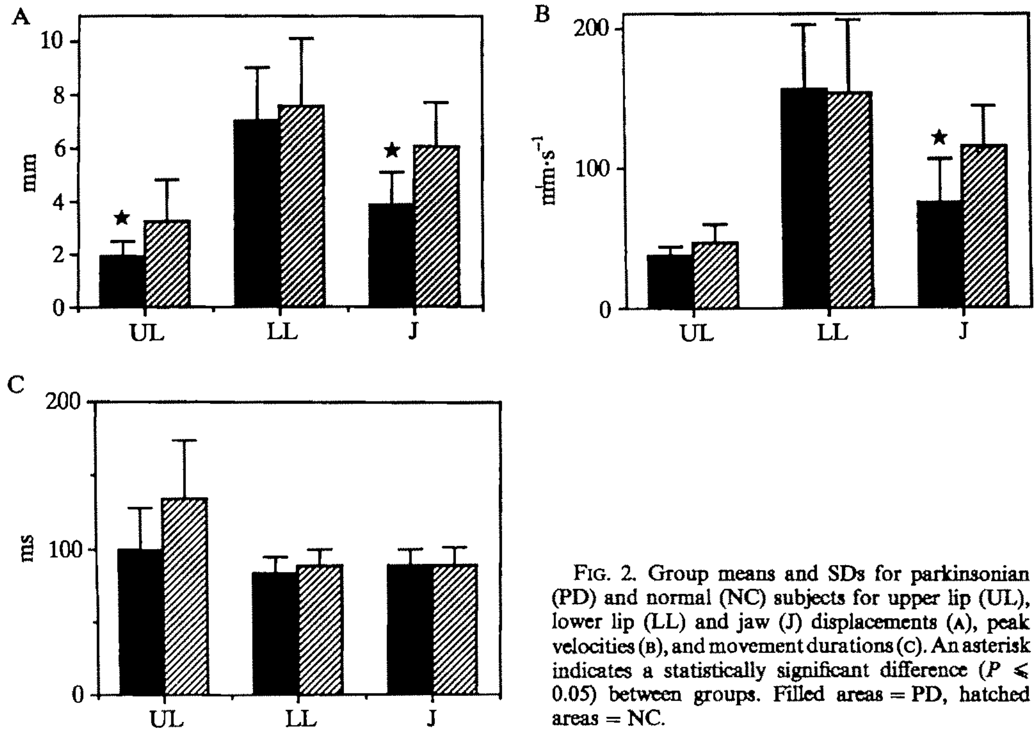

FIG. 2. Group means and SDs for parkinsonian (PD) and normal (NC) subjects for upper lip (UL), lower lip (LL) and jaw (J) displacements (A), peak velocities (B), and movement durations (C). An asterisk indicates a statistically significant difference ($P \leq 0.05$) between groups. Filled areas = PD, hatched areas = NC.

both kinematic measures, indicating nonuniform dysfunctions among structures. Post hoc comparisons (least significant differences) revealed uniform impairments for UL and J displacement and peak velocity ($P \leq 0.05$), while LL function on these measures was within the normal range. For peak velocity data, UL functioning was also not significantly different from the LL, which parallels findings from the group comparisons reported earlier. These direct comparisons document nonuniformity of function among these three orofacial structures. Specifically, the LL was not different from normal, while the UL and J manifested reduced displacements and/or peak velocities.

Interstructure coordination

Differential UL, LL, and J function had obvious consequences for coordination patterns. Fig. 3 shows the percentage contribution of each of the three oral movements to the total oral closing displacement for both groups (e.g., (UL/[UL+LL+J])·100). For the PD group, the LL contributed significantly more than normal (Mann-Whitney W = 112, $P = 0.02$) towards total oral closing, while UL and J percentage contributions each contributed less, although not at statistically significant levels. Contrary to expected results, fig. 3 suggested greater variability among the normal subjects on this measure. When quantified with coefficients of variation (CV), percentage contribution data were slightly more variable within normal subjects (mean CV: 0.183 UL, 0.72 LL, 0.106 J) than within the PD group (mean CV: 0.166 UL, 0.058 LL, 0.101 J). Although group CV differences are small and do not allow definitive conclusions, movement limitations within PD subjects may restrict variability in the execution of orofacial movements for speech.

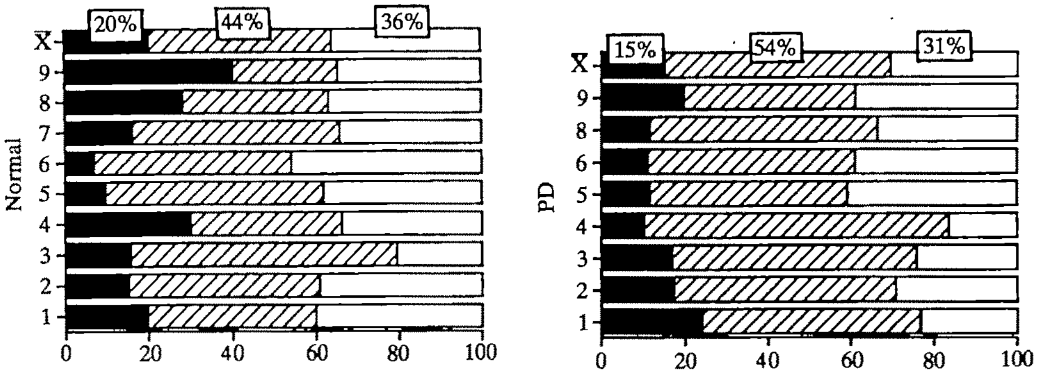

FIG. 3. The percentage each structure (i.e., upper lip (UL, filled areas), lower lip (LL, hatched areas), or jaw (J, open areas)) contributed to the total movement (UL + LL + J) in each group. The PD subjects used significantly more LL movement than within the normal data.

A second measure of coordination was movement sequencing among the lip and jaw components during oral closure. Previous work with normal subjects demonstrated a highly stereotyped pattern of UL, LL and J movement sequencing, where UL movement onsets and peak velocities preceded those for the LL, which in turn preceded those of J (Gracco and Abbs, 1986; Caruso, *et al.*, 1988). In this study, only the sequence of LL and J velocity peaks was examined in relation to coordination patterns because of the methodological problems in validly determining time of UL peak velocity noted previously. Interestingly, while timing patterns were observed to be highly uniform, movement amplitudes were variable within the normal speakers, suggesting independent neural control processes underlying timing and movement amplitude.

In the normal subjects, as in the earlier studies, LL peak velocity typically preceded that of the J. In contrast, LL and J velocity maxima in the PD subjects occurred simultaneously, or manifested a reversal of the stereotypic pattern observed in the normal subjects. To quantify these LL–J intervals, time of peak velocity for the LL was subtracted from that for the J. Fig. 4 presents data for all PD and normal subjects on this measure. Positive values were typically found for the normal subjects, indicating that LL peak velocities generally occurred prior

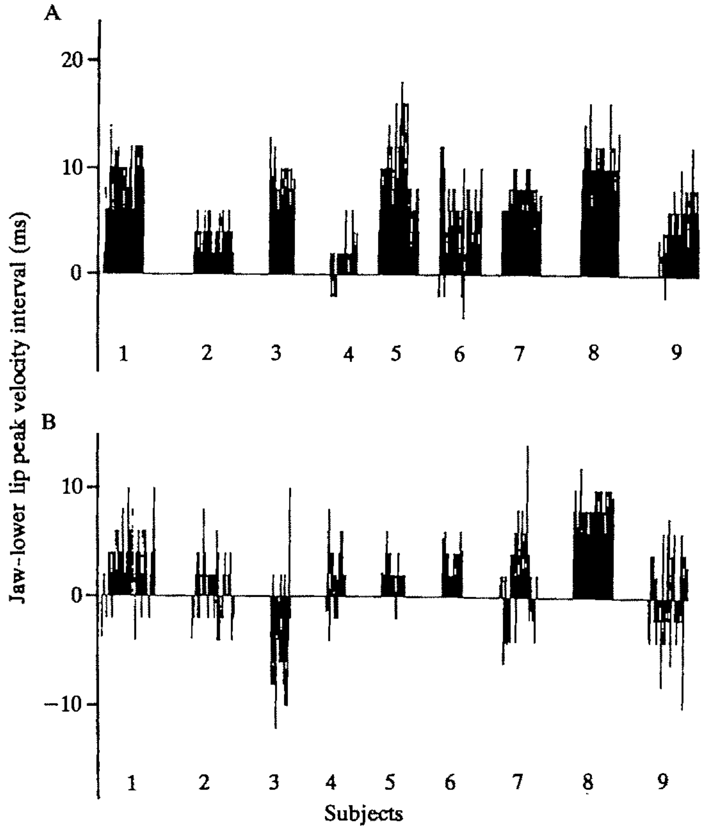

FIG. 4. The time between lower lip (LL) and jaw (J) peak velocities for all data collected for each subject. The normal data (A) tended to be positively orientated, indicating that LL velocity maxima occurred before those of the J. In contrast, the parkinsonian (PD) subjects (B) had significantly more reversals in this stereotypic pattern and tended to have velocity peaks occurring simultaneously.

to the J. For the PD subjects, however, significantly more reversals in this pattern were observed (Mann-Whitney test: W = 111, $P = 0.03$). The mean time between LL and J peak velocities was also significantly less in the PD group relative to normal, indicating greater synchrony of movement between the two structures in the former group and an apparent aberration in coordination ($t = 3.21$, $P = 0.006$).

DISCUSSION

Notable results from the present work included selective reductions in movement displacement, an absence of deficits in movement duration, and bradykinesia confined only to jaw movements in PD subjects. Similar findings have been suggested in part by other studies of speech movement abnormalities in PD (Hirose *et al.*, 1981, 1982; Hunker *et al.*, 1982; Caligiuri, 1987). However, results from these studies have been inconsistent. The current report thus adds new insights into the degree and nature of PD-related speech movement deficits, in that differences among multiple muscle groups and their interactions were detailed.

One result of note was that lower lip movements were not impaired in these PD subjects for this speech motor task. The absence of impairment in lower lip muscles was further evidenced by the fact that lower lip movement amplitudes were disproportionately greater in the PD subjects than normal (in relation to the combined UL, LL, and J movement). The PD subjects' ability to increase lower lip movement as a means of compensating for reduced jaw and upper lip movement strongly suggests normal control for this muscle group. A second indication of differential orofacial muscle group impairment was apparent in terms of bradykinesia, or reduced velocity. Despite ubiquitous reports in previous work of PD limb bradykinesia, in this study peak velocity was reduced only in the jaw. Interestingly, the muscles of jaw closing are similar to those of the limbs in that both have muscle spindles. Labial muscles, on the other hand, lack muscle spindles. Possibly the comparable finding of bradykinesia in jaw and limb muscle groups is related in some manner to aberrant spindle function. This notion is consistent with recent claims of proprioceptive dysfunctions during motor tasks in PD subjects (Schneider *et al.*, 1986, 1987; Viallet *et al.*, 1987). Abbs *et al.* (1987) reported parallel but somewhat different impairment profiles in isometric force control among muscle groups of the lips, tongue, and jaw. In that study, the combined lip muscles (upper and lower) manifested greater impairment than the jaw. However, that study involved only the examination of isometric contraction force control, while the present work analysed the movements of several structures towards a common goal. It would seem that motor impairments in the jaw may not be manifest for static (isometric) tasks; obviously, only with movement does the jaw's inertia have an influence. Interestingly, most proximal limb segments manifesting bradykinesia in PD also have significant inertia. When the movements of structures differing substantially in attendant inertia, such as those of the eye and hand, were compared directly, the hand with its greater inertia was observed to manifest earlier and greater PD impairment (Warabi *et al.*, 1986).

The present study adds evidence to the suspicion that there are some manifestations of discoordination in the movements of parkinsonian patients. The few existing kinematic studies of PD speech have not addressed the issue of coordination (Hirose *et al.*, 1981, 1982; Hunker *et al.*, 1982). The finding of significantly more reversals in the normal sequence of lower lip and jaw peak velocities in the PD group, as well as their greater synchrony, suggests an aberration in one aspect of interstructure coordination during speech movements. It is of interest that a similar aberrant pattern was found during fluent speech of stutterers, a speech disorder thought to reflect multiple structure discoordination (Caruso *et al.*, 1988). These findings are also consistent with suggestions of motor coordination disorders in limb movements of PD subjects (Hallett *et al.*, 1977; Sanes and Evarts, 1985). Other possible reflections of PD discoordinations have been reported, including nonrhythmic activity between arm swing and step phase for locomotion (Buchthal and Fernandez-Ballesteros, 1965) and for postural adjustments in lifting (Horak and Nashner, 1983). Overall, the nature of these subtle coordination disruptions is not easy to interpret. They may be compensatory, to maintain normal duration, or part of a more widespread impairment in selecting appropriate temporal features and/or scaling amplitude levels that have been seen in limb motor systems (Berardelli *et al.*, 1986).

Some of the findings of the present study may not be predictable from most previous studies of limb movement in PD. The present data generally support the position that PD motor impairments may vary with different motor tasks or different muscle groups. In part, this may be due to the fact that most recent studies of kinematic impairments in PD have involved upper limb movements to fixed spatial targets. By contrast, when lower limb displacements were examined during natural movements for locomotion, reduced stride length was accompanied by increased duration and reduced speed of forward progression (Knutsson, 1972; Knutsson and Martensson, 1986). The normal UL, LL, and J movement durations observed in this study are in contrast to those reports, as well as distinct from longer movement times reported in arm movement studies (Sanes, 1985; Berardelli *et al.*, 1986; Benecke *et al.*, 1987). Because fixed spatial targets do not appear to be implicit in speech (*cf.* Abbs *et al.*, 1984; Abbs, 1986; Gracco and Abbs, 1986), the present results highlight the influence of such motor task variables on the deficits observed. It is possible that sequential movements for behaviours such as speech are inherently controlled with primary emphasis on relative movement durations. Alterations in this important parameter could affect the distinctiveness of certain features of the speech acoustic signal. For example, varying the duration of certain acoustic segments can alter listener identification of consonants (Stevens and Klatt, 1974; Lisker, 1978). The normal word, phrase and sentence durations previously reported in acoustic analyses of PD speech support this notion (Ludlow and Bassich, 1983, 1984; Ludlow *et al.*, 1987). These apparent task-dependent differences in motor performance underline the need for studies with a greater variety of motor tasks, which may reveal some new perspectives on the factors underlying movement deficits in PD.

In summary, the present study indicates that analyses of a wider set of motor behaviours may complicate a previously simple view of the specific movement deficits in PD. For example, it is apparent that bradykinesia is not a universal feature of this disease. Likewise, it is not possible to rule out other problems such as discoordination nor to assume that all muscle groups manifest comparable patterns of deficit. Careful analyses of motor deficits for a variety of tasks and muscle groups may, however, help to resolve some of the apparent mysteries of this disorder. As was apparent in the present study, elongated duration of PD movements may be a phenomenon specific to visually-guided, target-specific limb movements and hence not manifest in sequential movements for speech. Also, bradykinesia may be manifest primarily in muscle groups in which the inertia of the structure to be moved is relatively large, such as the jaw or the forearm. Studies that address these and related hypotheses are necessary to appreciate fully the obvious complexity of this motor disorder.

At present, the basic research literature on motor contributions of the basal ganglia offers few insights into this problem (*cf.* Lidsky *et al.*, 1985). For example, some studies suggest that the basal ganglia contribute primarily to adjustments after movement initiation, while others indicate involvement in motor programming before the movement is executed (Aldridge *et al.*, 1980; Beaubaton *et al.*, 1980; Viallet *et al.*, 1981; DeLong *et al.*, 1983; Georgopoulos *et al.*, 1983; Crutcher and DeLong, 1984*a*, *b*; Liles, 1985; Alexander *et al.*, 1986). Likewise, it is not clear whether the basal ganglia contribute to specification of individual muscle contractions (Hore and Vilis, 1980; Horak and Anderson, 1984*a*, *b*), or to the much more general control of movement direction, independent of individual muscle activities (Iansek and Porter, 1980; DeLong *et al.*, 1983; Georgopoulos *et al.*, 1983; Crutcher and DeLong, 1984*a*, *b*). Some of these variations appear to be task specific. In this vein, invasive studies of basal ganglia function may yield more congruent conclusions regarding the function of this brain centre if animals are observed on a variety of motor tasks and if muscle groups other than those associated with the proximal upper limbs are studied. Certainly work of this kind is forthcoming and will be useful in addressing these issues.

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DIFFERENT INTERHEMISPHERIC TRANSFER OF KANJI AND KANA WRITING EVIDENCED BY A CASE WITH LEFT UNILATERAL AGRAPHIA WITHOUT APRAXIA

by MITSURA KAWAMURA,[1] KEIZO HIRAYAMA[1] *and* HARUMI YAMAMOTO[2]

(*From the* [1]*Department of Neurology, School of Medicine, Chiba University, Chiba, and* [2]*Department of Rehabilitation, School of Medicine, Showa University, Tokyo, Japan*)

SUMMARY

Recent neuropsychological studies have revealed that the processing of kanji (the Japanese morphograms) and kana (the Japanese syllabograms) involves different intrahemispheric mechanisms. We describe a patient showing left unilateral agraphia without apraxia for kanji, but not for kana, who was diagnosed by magnetic resonance imaging as having a lesion of the posterior body of the corpus callosum. This patient indicates that different neural pathways are used for kanji and kana not only intrahemispherically, but also interhemispherically.

INTRODUCTION

The written Japanese language is unusual in having two distinct sets of written characters, the kanji (which are the structurally complex morphograms often having several phonetic readings) and the kana (which are the relatively simple syllabograms having unambiguous phonetic readings) (Paradis *et al.*, 1985). Both kanji and kana are used in all sorts of printed matter, such as newspapers, magazines and books. In schooling, all of the kana (46 characters) and some of the simpler kanji are taught in the first year of elementary school, whereas use of the approximately 1900 kanji prescribed by the Ministry of Education is taught during the first 9 years of education.

All kanji can be represented phonetically in kana. For example, 命 (character No. 4 in fig. 3) can also be depicted as いのち (pronounced inochi). In writing sentences, kanji and kana are typically combined together such that the major lexical morphemes are written in kanji, while conjugated endings of verbs and adjectives, as well as function words, are always written in kana.

That the left cerebral hemisphere is responsible for the reading and writing of

Correspondence to: Dr M. Kawamura, Department of Neurology, School of Medicine, Chiba University, 1-8-1 Inohana, Chiba 280, Japan.

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both kanji and kana has already been demonstrated (*see* Iwata, 1984, and literature citations therein). Recently, however, neuropsychological studies have revealed that the processing of kanji and kana involve different intrahemispheric mechanisms. For example, lesions to the inferior portion of the left inferior temporal gyrus in Japanese patients have been shown to lead to alexia and agraphia specific to kanji (e.g. Iwata, 1984, 1986; Kawamura *et al.*, 1987). Lesions of the left parietal lobe can produce selective agraphia for kana (Tanaka *et al.*, 1987) and Japanese deep dyslexics have been found to be able to read kanji, but not kana (Sasanuma, 1980).

In the present study we report a patient with left unilateral agraphia for kanji without apraxia, who was diagnosed by magnetic resonance imaging (MRI) as having a lesion of the posterior body of the corpus callosum. This patient illustrates the possibility that not only are there *intra*hemispheric differences in the processing of kanji and kana, but that there are different *inter*hemispheric pathways in use for these two different writing systems.

CASE REPORT

A 74-yr-old right-handed man with 9 yrs of formal education developed right-sided motor paresis and urinary incontinence on June 22, 1986. On the same day, he was admitted to hospital where a diagnosis of cerebral infarction was made on the basis of a CT scan. In digital subtraction angiography (DSA), occlusion of the origin of the left pericallosal artery was identified. On August 23, he was transferred to the Department of Neurology of Chiba Rosai Hospital.

Neurologically, he was fully conscious and orientated at the time of admission. Pursuit and saccadic ocular movements, optokinetic nystagmus and corrected visual acuity were normal. Goldmann perimetry confirmed full visual fields. There was no visual inattention to double simultaneous stimulation and other cranial nerve functions were intact. Right-sided motor paresis was found, together with accelerated tendon reflexes. There was a grasp reflex in the right hand and the plantar responses were extensor bilaterally. The appreciation of heat and pain was slightly reduced on the right side.

Neuropsychologically, the patient had normal auditory comprehension, showed no abnormalities in a naming test of familiar objects, and he was not aphasic. There was no indication of hemineglect (bisection of a line, copying pictures of a house with trees (fig. 1), and Albert's line-crossing test). Moreover, copying a diamond shape, a Greek cross and a cube with either the left or right hand was normal. Drawing from memory (airplane, map of Japan, dog, ship, etc.) with either the left or right hand was normal (fig. 2). Facial recognition, identification of overlapping figures (Poppelreuter), colour naming, left-right discrimination, finger naming and simple verbal calculations were intact.

Aspects of the callosal disconnection syndrome, such as agraphia, apraxia and tactile anomia of the left hand, and crossed optic ataxia, were found. Using the left hand, there were clear abnormalities when pantomiming the use of common objects, such as a comb, toothbrush, bottle-opener, spoon, cigarette, etc. In a test for tactile anomia, he scored 16/16 with the right hand in using common objects, but only 7/18 with the left hand. The apraxia and optic ataxia disappeared within 4 months, but notable agraphia of the left hand remained. His Wechsler Adult Intelligence Scale score was at an average level (Verbal IQ = 113, Performance IQ = 80, Full Scale IQ = 100).

As from April and May, 1987 (10–11 months after onset), his spontaneous speech was well articulated and fluent without paraphasic errors. On the Western Aphasia Battery (WAB) profile of speech (Sugishita *et al.*, 1980; Kertesz, 1982), he was rated as normal, and there were no errors on the WAB tests of spontaneous speech, auditory comprehension, repetition or reading.

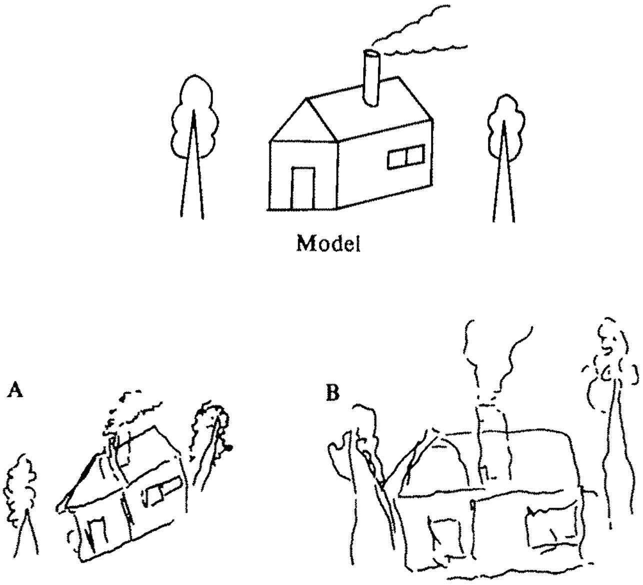

FIG. 1. The picture used for the copying test. The patient's drawings show little difference using the right (A) and left (B) hands.

Standardized writing tasks were also given in April and May, 1987 (10–11 months from onset). On the Japanese version of the WAB tests, his writing scores were different using the right and left hands (10/10 and 7.25/10, respectively). These results reflected a deficit in spontaneous writing and writing to dictation specifically for kanji with the left hand. This finding is particularly significant in the light of the fact that kanji, which he could not write, were correctly replaced by the appropriate kana. In spontaneous writing and writing to dictation the WAB test, his performance was normal with the right hand when writing kana and only a very few errors were made with the left hand. In contrast, performance with the right hand was normal for writing kanji, but was very slow and accompanied by errors with the left. In writing to dictation with the left hand, sentences which included both kanji and kana were often written with the corresponding kana instead of kanji. When asked to write with the left hand the kanji that he had previously replaced by kana, he was unable to do so. Spontaneous writing and writing to dictation with the right hand were completely normal.

Special writing tests to examine the relative disturbance of kanji and kana were then administered. He was asked to write with both the left and right hands 160 kanji characters in response to dictation

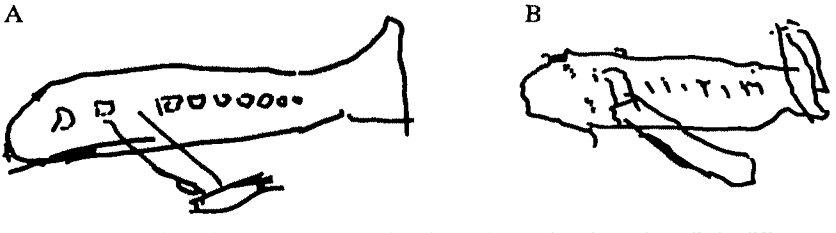

FIG. 2. Drawing of an airplane from memory. Again, the patient's drawings show little difference using the right (A) and left (B) hands.

and then the corresponding 160 kana words, all of which had been learned in the first 3 years of primary education (Table, fig. 3). The writing errors were categorized into the following five types: (1) no response; (2) partial completion, in which a portion of the correct character was written, but the entire kanji or kana was not completed; (3) partial substitution, in which a portion of the required kanji or kana was replaced with strokes which were incorrect, but frequently found among actual kanji or kana; (4) substitution, in which an incorrect but complete character was written; and (5) neographism, in which it was not possible to identify an existing character in the writing produced. For substitutions and partial substitutions, the error was further classified into one of four categories depending upon its visual, phonological, semantic or lack of relationship with the target. We are aware of the fact that there may be no sound basis on which to compare performance on kanji and kana, but our major interest here lies in a comparison of the number of kanji errors made when using the right and left hands, as well as a comparison between the hands when writing kana.

TABLE. A COMPARISON OF THE DEFICITS IN WRITING KANJI AND KANA TO DICTATION*

	Kana		*Kanji*	
Error	*Right*	*Left*	*Right*	*Left*
No response	0	0	0	1
Partial completion	0	0	0	16
Partial substitution				
Visual	0	0	0	25
Phonological	0	0	0	0
Semantic	0	0	0	1
Unrelated	0	0	0	1
Substitution				
Visual	0	2	0	0
Phonological	0	0	0	1
Semantic	0	0	0	0
Unrelated	0	2	0	0
Neographism	0	0	0	2
Total no. of errors	0	4	0	47

* The results of a comparison of the errors made in response to dictation of 160 kanji and the 160 corresponding kana words are shown. No deficits for the right hand were found. A significant difference between the left and right hands in the writing of kana was not detected, but a highly significant difference was found for the writing of kanji ($\omega^2 = 1.70$ E+38, $P < 0.01$).

The kana and kanji writing was performed in randomized blocks of 10 or 20 with each hand in order to minimize any short-term practice effects. The actual order was 10 kana with the right hand, 10 kanji with the left, 10 kanji with the left, 10 kana with the right, and so on.

In writing kana, the right hand was completely normal, but the left produced a small number of errors (4/160, 2.5%), 2 of which were substitutions with kana that were visually similar to the target and 2 of which were unrelated to the target. The difference between the left and right hands in writing kana was not statistically significant. In writing kanji, again no errors were made with the right hand, but many errors were made (47/160, 29.4%) with the left. This difference in performance between the left and right hands was highly significant ($\chi^2 = 1.70$ E+38, $P < 0.01$). Of the kanji errors, there was only 1 substitution of an actual kanji for the required character, 1 no-response and 2 neographisms. The majority of the errors were partial completions and partial substitutions. For partial substitutions, the most common mistake was the production of a kanji which was visually similar to the target.

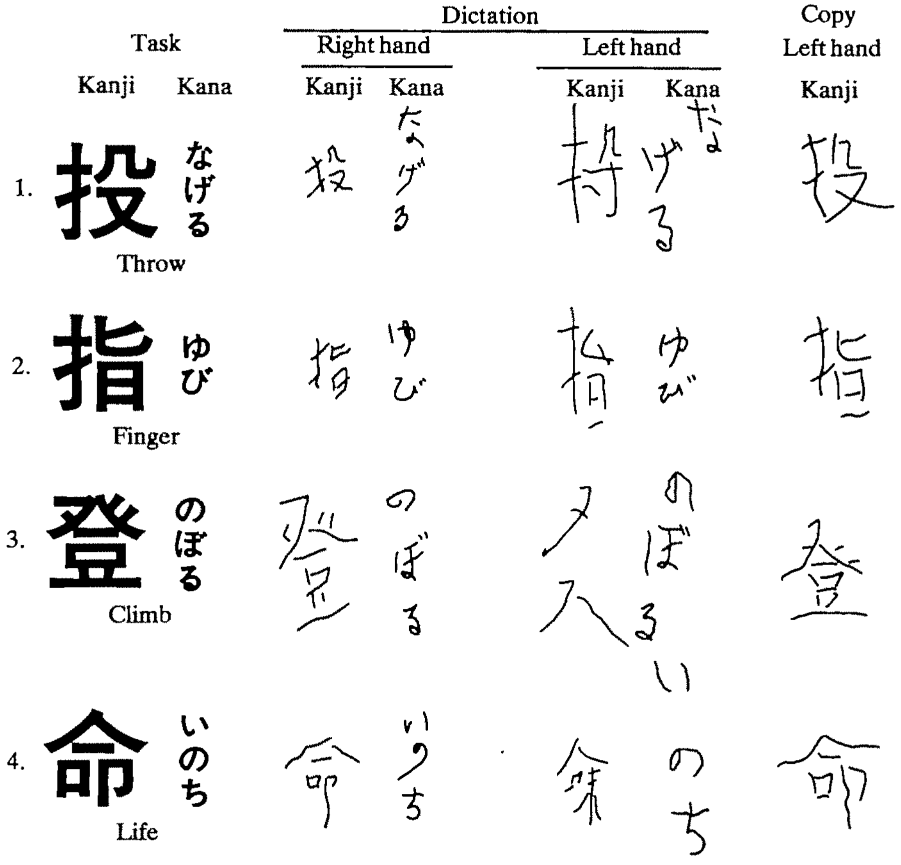

FIG. 3. Samples of deficits in writing kanji. Errors were produced only with the left hand in response to dictation. Copying of the same kanji with the left hand was unimpaired. Mistakes (1) and (2) are examples of plausible partial substitutions, (3) is a partial completion (this error represents a second attempt at writing the upper portion of 'climb', and (4) is a neographism. The patient occasionally noticed his own mistakes, but usually could not produce the correct kanji even with repeated efforts (e.g., 3).

For anatomical localization of the lesion, x-ray computed tomography (CT) and magnetic resonance imaging (MRI) were used. In a CT slice located 10 cm above the orbitomeatal line (September 25, 1986), 2 small elliptical low density areas on the medial surface of the parietal lobe and continuous with the left and right lateral ventricles were seen. MRI was performed with a Picker 0.5 Tesla superconducting MR imager using the inversion recovery technique on November 1, 1986. The width of the slice was 10 mm and the patient's head was positioned supine. Midsagittal imagings (fig. 4) showed a lack of the normal high intensity at the posterior part of the body of the corpus callosum. There were no abnormalities of the rostrum, splenium or anterior portion of the

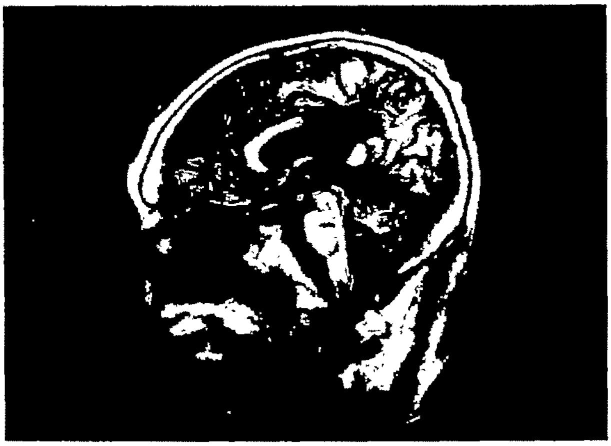

FIG. 4. Magnetic resonance imaging (132 days after symptom onset), inversion recovery, midsagittal view (time of repetition (TR) = 2080 ms, time of inversion (TI) = 500 ms). A distinct low intensity area is seen in the posterior half of the body of the corpus callosum, but the rest of the callosum (rostrum, genu, splenium and anterior half of the body) is normal. A faint low intensity area in the medial parietal lobe and the cingulate gyrus above the callosal lesion is also visible. .

body of the corpus callosum. Continuous with the callosal lesion, faint low density areas on the medial surfaces of the parietal lobes were seen bilaterally in both coronal and horizontal images.

DISCUSSION

Geschwind (1965) has previously suggested that left-sided agraphia is not merely a manifestation of apraxia, but is a sign of disturbed flow of linguistic information from the left hemisphere to the right. In order to prove such a hypothesis, however, it is necessary to demonstrate the disconnection of the (language-dominant) left hemisphere from the right hemisphere (which controls the left hand) due to a callosal lesion. The incidence of left unilateral agraphia without apraxia is extremely low, with only 4 such cases having been reported (Sugishita *et al.*, 1980; Yamadori *et al.*, 1980; Gersh and Damasio, 1981; Degos *et al.*, 1987).

Our patient showed deficits in spontaneous writing and writing to dictation with the left hand only and no disturbance in the copying of pictures or words (kanji and kana) with either hand. Left unilateral apraxia was also not found in response to verbal commands and praxic imitation. Our case is therefore the fifth reported case of left unilateral agraphia without apraxia, which demonstrates the validity of Geschwind's suggestion. Our case is also unusual in that the location of the lesion in the corpus callosum has been unambiguously shown with MRI.

The MRI technique provides a new and valuable tool for research on callosal function. Unlike x-ray CT scans, sagittal sections can be taken and lesions of the corpus callosum are extremely well-visualized in midsagittal sections (e.g., Kawamura *et al.*, 1985*a*, *b*; Watson *et al.*, 1985; Graff-Radford *et al.*, 1987). For example, one of Gazzaniga's patients who had been thought to have undergone total callosal section was shown by MRI to have part of the corpus callosum still intact (Gazzaniga *et al.*, 1985). The MRI findings in our patient showed a callosal lesion confined to a small region of the posterior part of the body of the corpus callosum with no other abnormalities.

Iwata (1984, 1986) and ourselves (Kawamura *et al.*, 1987), among others, have previously reported that selective deficits in the reading and writing of kanji are produced by lesions of the left posterior inferior temporal gyrus. It has also been reported that lesions of the left parietal lobe can produce selective agraphia for kana only (Tanaka *et al.*, 1987). Moreover, Sasanuma (1980) has shown that Japanese deep dyslexics can read kanji, but not kana. In general, the agraphia found in Japanese aphasics is more severe for kana than for kanji (Paradis *et al.*, 1985). It is thus apparent that, independent of the fact that kanji are graphically more complex than kana, the two writing systems in Japanese can be selectively impaired. In other words, it has been shown that different pathways within the left hemisphere are used for the writing of kanji and kana.

Among the 4 previously reported cases of left unilateral agraphia without apraxia, localization of the lesion to callosal fibres was possible in the surgical case of Sugishita *et al.* (1980) and in the case reported by Gersh *et al.* (1981) resulting from a haemorrhage. In both cases, the lesion was localized to the posterior part of the body of the corpus callosum, similar to our own case. The lesion in the case of Degos *et al.* (1987) was also confirmed pathologically to the posterior part of the callosal body, extending into the splenium. Including our own case, these 4 cases clearly indicate that the communication of writing functions between the cerebral hemispheres takes place through the posterior part of the callosal body.

Particularly noteworthy in our patient was the fact that the writing deficit did not include significant differences between the left and right hands in the writing of kana, but did involve a marked agraphia of the left hand when writing kanji. Moreover, among the kanji errors produced (*see* Table), there was only 1 substitution and 1 no-response. Most errors consisted of correctly writing a portion of the kanji, but leaving it incomplete, or writing a complete kanji with plausible but incorrect portions. These findings indicate that the linguistic information required for writing kanji is being incompletely transferred from the left hemisphere to the right.

Two of the 4 previously reported cases with this syndrome were also Japanese (Sugishita *et al.*, 1980; Yamadori *et al.*, 1980). Unlike our patient, however, writing deficits were found both for kanji and kana, and were predominant for kana. It is likely that the differences among these patients are due to differences in the site and spread of the lesion. Individual differences in callosal function may also be involved.

The results obtained from the present case strongly suggest that, in addition to different *intra*hemispheric pathways, distinct *inter*hemispheric pathways via the corpus callosum are employed for the writing of kanji and kana.

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ANTERIOR CALLOSAL HAEMORRHAGE

A PARTIAL INTERHEMISPHERIC DISCONNECTION SYNDROME

by RAMON LEIGUARDA, SERGIO STARKSTEIN[1] *and* MARCELO BERTHIER

(*From the Instituto de Investigaciones Neurologicas Dr R. Carrea-Fleni, Buenos Aires, Argentina*)

SUMMARY

The interhemispheric disconnection syndrome secondary to a callosal haemorrhage is exceedingly uncommon. In the present study, 3 patients with haemorrhages restricted to the corpus callosum are presented. All 3 developed a partial anterior interhemispheric disconnection syndrome: unilateral tactile anomia, unilateral agraphia, unilateral apraxia, difficulty in copying drawings, dyscalculia as well as abnormalities of somaesthetic transfer and the 'alien hand' sign. The study of these cases allowed a close examination of the association between deficits in the transfer of specific neuropsychological information and the precise topography of callosal damage. Variability in the lateralization of cognitive functions, and possible mechanisms underlying the production of callosal haemorrhages after the rupture of saccular aneurysms are also discussed.

INTRODUCTION

Knowledge concerning the neurological and psychological effects of callosal disconnection stems mostly from observations of patients whose neocortical commissures were sectioned as treatment for severe epilepsy (Sperry *et al.*, 1969; Bogen, 1985). Since damage to the corpus callosum rarely occurs in isolation, and damage of adjacent structures may mask symptoms pertaining to callosal involvement, the callosal disconnection syndrome is seldom the result of naturally occurring lesions. Clinical cases contributing to the interpretation of the callosal disconnection syndrome have fallen mainly in two groups: (1) those with occlusion of the anterior cerebral artery or one of its branches; and (2) those with invasive neoplasms of the corpus callosum (for review, *see* Brion and Jedynak, 1975).

Haemorrhages into the corpus callosum are relatively rare and mainly found within the context of more extensive cerebral damage, often secondary to bleeding from a vascular malformation (Crompton, 1962; Brion and Jedynak, 1975; Escourolle *et al.*, 1975; Yock and Larson, 1980; Lau *et al.*, 1984). Only 9 cases of interhemispheric disconnection syndrome due to callosal haemorrhages have so far been reported. Five cases had haemorrhages in the posterior portion of the

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Correspondence to: Dr R. Leiguarda, Instituto de Investigaciones Neurologicas Dr R. Carrea-Fleni, Ayacucho 2166, 1112 Buenos Aires, Argentina.

[1] Present address: Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Meyer Building 4-119, Baltimore, MD 21205, USA.

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callosum (4 secondary to an arteriovenous malformation (Brion and Jedynak, 1975; Gersh and Damasio, 1981; Yamadori *et al.*, 1983) and 1 of traumatic origin (Alexander and Warren, 1988)), whereas 4 had haemorrhages secondary to ruptured saccular aneurysms involving the anterior half of the callosum (Sweet, 1945; Brion and Jedynak, 1975; Poncet *et al.*, 1978; Graff-Radford *et al.*, 1987).

We report 3 patients with haemorrhages restricted to the corpus callosum who developed a partial callosal disconnection syndrome as the main complication of the haemorrhagic lesions.

PATIENTS

Case 1

A 57-yr-old right-handed male (+100 on Handedness Inventory, Oldfield, 1971) suddenly developed severe bilateral frontotemporal headache, nausea and vomiting. Two weeks later he was admitted to our unit complaining of headache, gait difficulties and urinary incontinence. On neurological examination the patient was alert and fully orientated; his digit span was 6 numbers forward and 3 backwards. General information for past events was unaffected; he showed no impairment in learning new material and no confabulation was observed spontaneously or in response to specific questions. Although spontaneous speech was well articulated and grammatical, he experienced difficulties in initiating conversation and showed long response latencies as well as hypophonia. Naming, repetition, auditory and reading comprehension were normal. He had signs of callosal dysfunction (*see* Neuropsychological Assessment). Mild neck stiffness was present. Cranial nerve examination proved normal and there was no evidence of hemianopia or visual

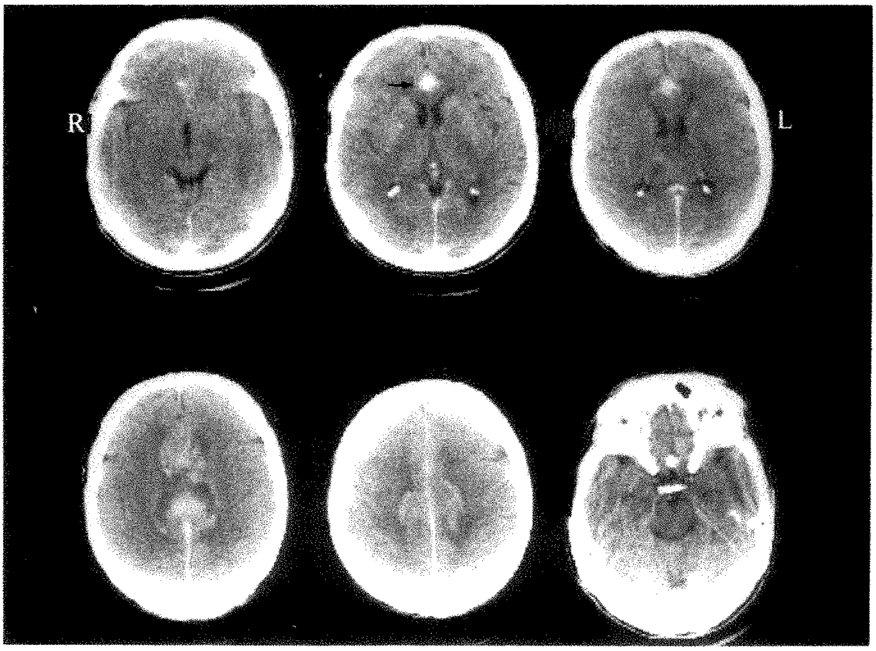


FIG. 1. *Case 1.* Postcontrast CT scan showing a resorbing callosal haemorrhage with peripheral enhancement (pseudotumoral pattern). Arrow indicates a saccular aneurysm.

inattention. There was mild weakness in both lower limbs with increased tendon reflexes. An extensor plantar response was elicited on the left, and a tonic foot response was present on the right. There was also a right hand grasping reflex, but no other motor deficit in either arm. Sensation was normal and the patient could adequately identify single or double tactile simultaneous stimulation on either limb. Two weeks after onset, a CT scan revealed a lesion of increased attenuation involving the corpus callosum from the dorsal-rostral portion of the genu to the most caudal part of the body (fig. 1). After the injection of intravenous contrast material an irregular peripheral enhancement of the lesion was observed, a finding consistent with the 'pseudotumoral pattern' characteristic of a reabsorbing callosal haemorrhage (Lau *et al.*, 1984).

There was no radiological evidence of extracallosal damage. CT measurement of skull asymmetries demonstrated the typical left occipital 'petalia' (Hadziselimovič and Čuš, 1966) normally observed in right-handed individuals (Pieniadz *et al.*, 1983). While mean occipital widths and lengths were +20 and +10, respectively, frontal region measurements showed symmetric widths and lengths.

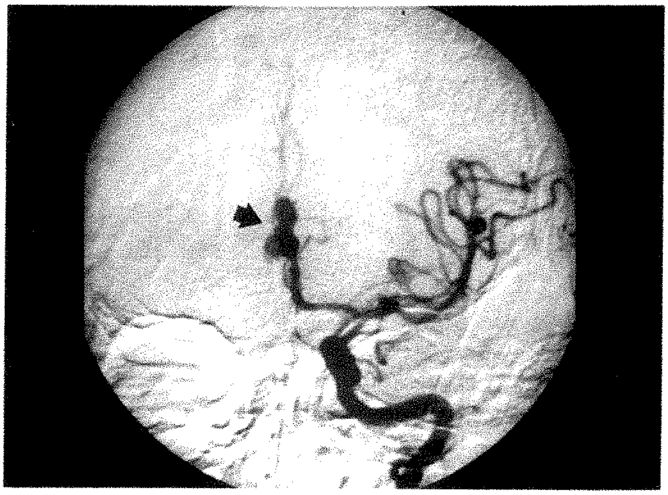


FIG. 2. *Case 1.* Digital subtraction angiography demonstrating a saccular aneurysm (arrow) at the right pericallosal bifurcation, displacement of the callosomarginal artery towards the left, and stretching and straightening of the pericallosal artery with mild vasospasm.

Digital subtraction angiography showed a bilobulated saccular aneurysm at the right pericallosal bifurcation. The callosomarginal artery was slightly displaced towards the left, and the pericallosal artery was stretched and straightened, showing mild vasospasm (fig. 2). The patient refused surgery and died a week later, presumably due to massive rebleeding. No postmortem examination was available.

Case 2

A 51-yr-old ambidextrous male (+40 on Handedness Inventory, Oldfield, 1971) with a family history of sinistrality suffered a sudden severe frontal headache and immediately fainted. He recovered consciousness after 25 min but felt dizzy and was admitted to hospital. Past history was unremarkable. On examination the patient was alert and orientated in time, place and person. Attention and memory were normal. His spontaneous speech was abnormally sparse with long pauses but with preserved articulation and grammar. Naming, repetition, and auditory and reading comprehension were also normal. He had signs of callosal disconnection (*see* Neuropsychological

Assessment). Cranial nerve examination was normal with no hemianopia. He had left crural hyperreflexia with a left extensor plantar response and forced grasping in both hands. Sensation and coordination were normal and there was no neck rigidity. A CT scan showed blood in the anterior interhemispheric fissure and a circumscribed haemorrhage extending from the dorsal part of the genu to the caudal third of the callosal body (fig. 3).

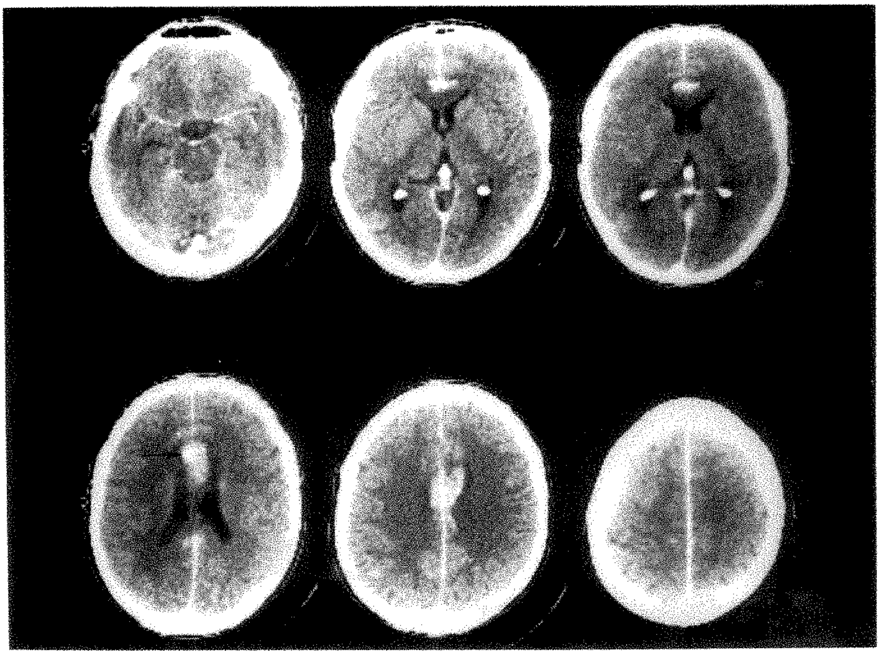


FIG. 3. *Case 2.* Postcontrast CT scan showing callosal haemorrhage. Arrow indicates a saccular aneurysm.

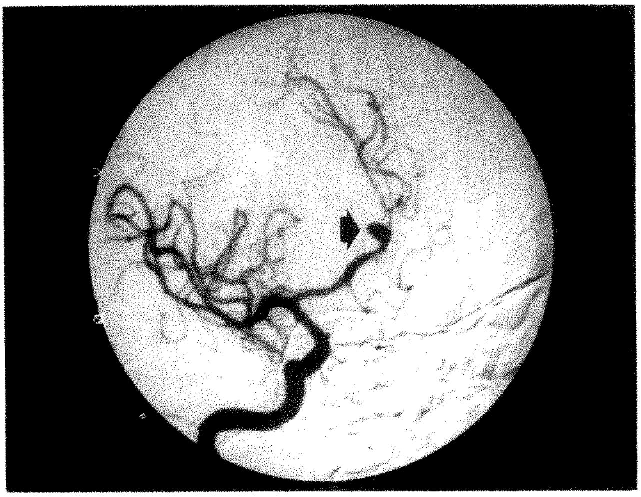


FIG. 4. *Case 2.* Digital subtraction angiography showing a saccular aneurysm (arrow) of the left pericallosal artery and stretching of the pericallosal artery with moderate vasospasm.

CT measurements of skull asymmetries (Pieniadz *et al.*, 1983) showed an 'atypical' pattern with a larger left frontal region (widths −40 and lengths −10) and a larger right occipital region (widths −30 and lengths −10). Digital subtraction angiography showed a saccular aneurysm of the left pericallosal artery at the junction with the callosomarginal artery. Stretching of the pericallosal artery as well as moderate vasospasm were also observed (fig. 4). The aneurysm was successfully clipped and the patient made a gradual recovery.

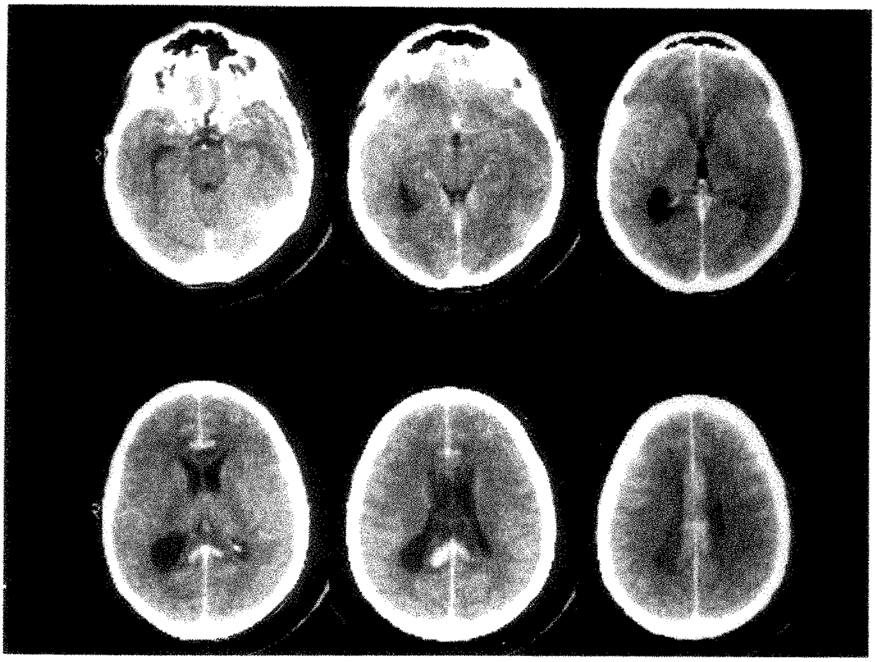


FIG. 5. *Case 3.* Postcontrast CT scan showing callosal haemorrhage. Arrow indicates a saccular aneurysm.

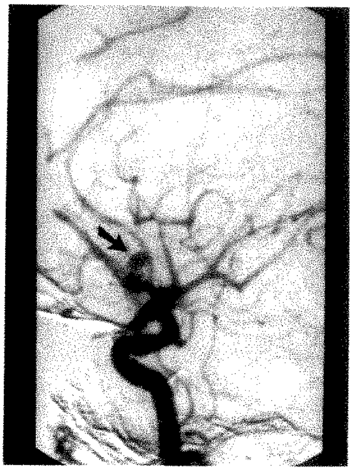


FIG. 6. *Case 3.* Digital subtraction angiography demonstrating a saccular aneurysm (arrow) of the anterior communicating artery and stretching of the pericallosal artery due to the intracallosal lesion with mild distal and segmented vasospasm.

Case 3

This case was extensively described in a previous report (Starkstein *et al.*, 1988) and only the main features will be presented here. A 35-yr-old right-handed male (+100 on Handedness Inventory, Oldfield, 1971) was admitted to hospital complaining of loss of speech fluency and antagonistic movements of the left hand (e.g., after having picked up a pen with his left hand, he could not transfer it readily to the right hand and was forced to take it with an effort). He also noticed that his left hand behaved in a noncooperative way (e.g., when he tried to open a drawer with his right hand, the left tried to close it). This behaviour was so astonishing and uncontrollable that he occasionally hit his left hand with the right one. All these symptoms had a sudden onset 15 days before his admission and were accompanied by headache, nausea, vomiting, dizziness and urinary incontinence, all of which cleared in 36 h. A month before hospitalization, however, the patient noticed a sudden and intense frontal headache that lasted a few hours. There was no personal history of neurological illness during infancy and no family history of left-handedness. On physical examination he was attentive, cooperative and fully orientated, but he had signs of callosal disconnection (*see* Neuropsychological Assessment). Memory was normal. His spontaneous speech was sparse, monotonous, agestural, and showed long response latencies. Naming, repetition, auditory and reading comprehension were all normal. Cranial nerves were normal. He had a mild paraparesis with bilateral flexor plantar responses, brisk tendon reflexes and forced grasping with his right hand. On double simultaneous tactile stimulation, extinction was found on the right side (upper limb). Coordination was normal and he had a slight nuchal rigidity. A CT scan showed an extensive haemorrhage involving the callosum from the rostral portion of the genu to the dorsal splenium (fig. 5). After contrast enhancement a small hyperdense mass was observed in the anterior portion of the suprasellar cistern. CT measurements of skull asymmetries (Pieniadz *et al.*, 1983) showed an 'atypical' pattern with a larger right occipital region (widths −20 and lengths −10), but with symmetric widths and lengths in the frontal region.

Digital subtraction angiography revealed a saccular aneurysm of the anterior communicating artery with stretching of the pericallosal artery due to the intracallosal lesion; mild distal and segmental vasospasm was also observed (fig. 6).

Neuropsychological assessment of callosal functions

A detailed neuropsychological evaluation of callosal function was performed in all 3 patients as follows.

Somaesthetic transfer. While blindfolded, one of the patients' upper limbs was put in a fixed position and they were asked to copy this position with the other limb. Later, both palms were placed upwards and the tip of one finger was slightly touched by the examiner; patients were asked to touch the corresponding finger of the contralateral hand using the thumb of that same hand. Five right-handed male normal controls (mean age 48.6 yrs) were also examined and their performance compared with the patient group.

Tactile naming. While blindfolded, patients were asked to palpate and name 10 common objects. Each hand was tested separately, and after each trial, patients were asked to recognize the object after it had been mingled with other unrelated ones.

Visual naming and reading (in each half visual field). Patients were asked to name 10 common objects to confrontation and to read aloud 10 words presented in either the left or right half visual fields.

Writing. Patients were asked to write and typewrite simple words and short sentences spontaneously, from copy, and to dictation. Left and right hands were tested separately.

Drawing. Patients were presented with four different geometric figures (cube, square, triangle and hexagon) and were asked to copy them. Each hand was tested separately.

Calculation. Patients were asked to carry out additions, subtractions, multiplications and divisions, both written and mentally.

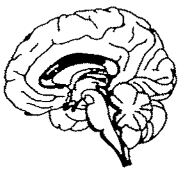
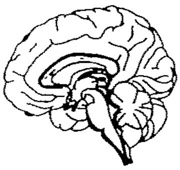
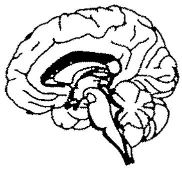
Praxis. Patients were asked to carry out transitive (involving direct manipulation of an object) and intransitive (not involving direct manipulation of an object) movements on command, then to imitate the examiner's movement and finally to demonstrate the use of an actual object. Whole body and buccofacial movements were also examined.

RESULTS

Results of the neuropsychological evaluation of callosal functions are listed in the Table and only the main findings will be described.

Somaesthetic transfer. On the first test (copy of the position of the contralateral upper limb), 4 normal controls performed flawlessly (10/10 correct), while 1 made 1 error (normal control group mean ±SD = 9.8±0.4). All 3 patients performed below chance and more than 4 SD below normal. On the contralateral finger recognition task, 3 normal controls performed flawlessly (10/10 correct), while 2 normal controls made 1 error (9/10 correct) (normal control group mean ±SD = 9.6±0.55). All 3 patients scored below chance level and more than 4 SD below the normal control group mean.

TABLE. RESULTS OF NEUROPSYCHOLOGICAL EVALUATION OF CALLOSAL FUNCTIONS

	Case 1	*Case 2*	*Case 3*
Somaesthetic transfer			
Cross-replication of hand postures	2/10	6/10	3/10
Cross-localization of finger tips	3/10	5/10	4/10
Tactile naming			
Right hand	10/10 correct	10/10 correct	0/10 correct
Left hand	0/10 correct	10/10 correct	10/10 correct
Visual naming	Normal	Normal	Normal
Writing			
Right hand	Normal	Aphasic agraphia	Aphasic agraphia
Left hand	Apraxic agraphia	Normal	Normal
Reading (in each half visual field)	Normal	Normal	Normal
Drawing			
Right hand	0/4 correct	4/4 correct	0/4 correct
Left hand	4/4 correct	0/4 correct	4/4 correct
Calculation			
Written	Impaired	Impaired	Impaired
Mental	Normal	Normal	Impaired
Praxis			
Right hand	Normal	Normal	Ideomotor apraxia
Left hand	Ideomotor apraxia	Normal	Normal
Alien hand sign	Present	Absent	Present
Autocriticism	Absent	Absent	Present
			

At the bottom of each patient column, the diagrams illustrate the rostrocaudal extent of the callosal haemorrhage based on CT sagittal reconstructions.

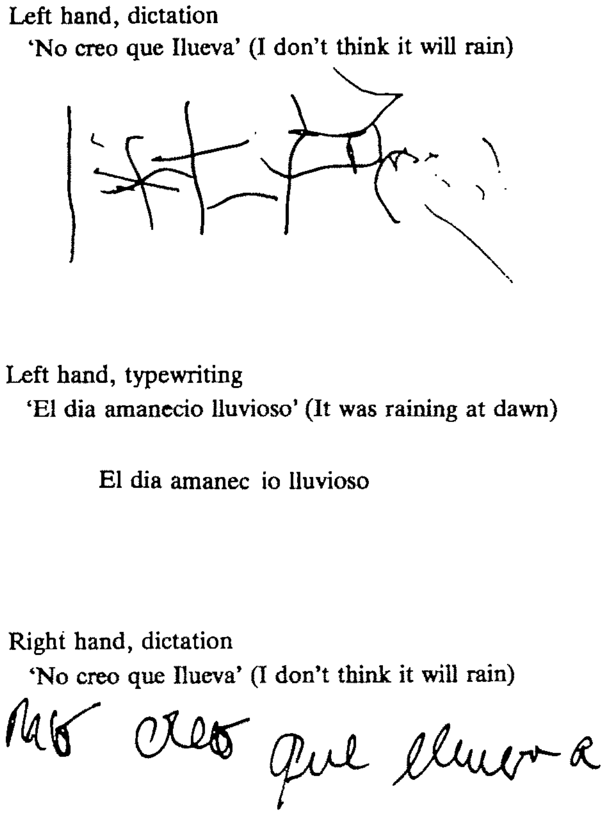

Left hand, dictation
'No creo que Ilueva' (I don't think it will rain)
Left hand, typewriting
'El dia amanecio lluvioso' (It was raining at dawn)
El dia amanec io lluvioso
Right hand, dictation
'No creo que Ilueva' (I don't think it will rain)
No creo que lluev-a

FIG. 7. *Case 1.* Left hand apraxic agraphia.

Tactile naming. Unilateral tactile anomia was demonstrable for the left hand in Case 1 and for the right hand in Case 3; they were unable to name any of the objects properly with these hands although they were able to recognize adequately all 10 objects by touching when they were mingled with 10 unrelated ones.

Writing. While all the patients showed unilateral agraphia, this was either an apraxic agraphia (e.g., an illegible scrawl) in Case 1 (fig. 7) or an aphasic agraphia (e.g., letters or syllable repetitions, distortions, omissions and inversions) in Cases 2 and 3 (figs 8, 9).

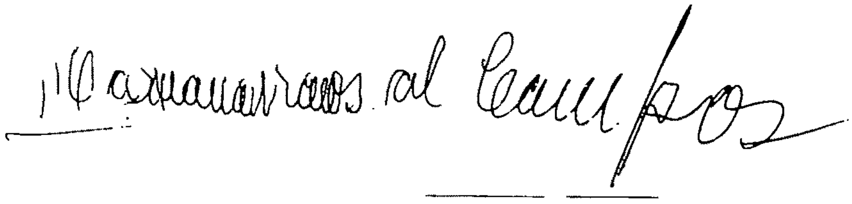
Drawing. All 3 patients showed unilateral copying difficulties, but none had any evidence of spatial neglect.

Calculation. Written calculation was impaired in all patients mainly due to difficulty in aligning columns of numbers, particularly in Case 1 (fig. 10). Mental calculation was preserved in Cases 1 and 2 but mildly impaired in Case 3.

Praxis. Only Cases 1 and 3 showed a unilateral ideomotor apraxia. On verbal command, Case 1 showed slow responses with his left hand characterized by irrelevant gestures. Errors were mainly observed in distal movements, particularly in those requiring the use of single digits. When performing movements that

Right hand, spontaneous writing

'Mañana iremos al campo' (Tomorrow we will go to the countryside)



Left hand, spontaneous writing 'lapicera' (pen)

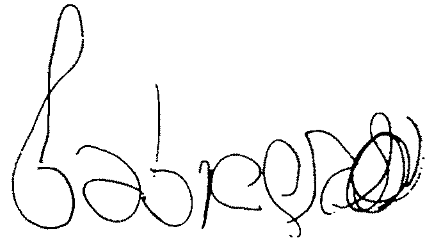
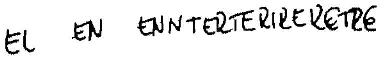


FIG. 8. *Case 2.* Right hand aphasic agraphia; left hand graphomotor disturbances attributable to left hand grasping.

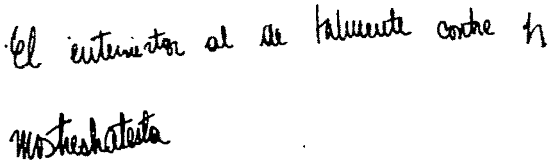
Right hand, spontaneous writing

'El interior' (The inside)



Right hand, dictation

'El interior de la habitacion mostraba...'
(The inside of the room showed..)



Left hand, dictation

'El interior de la habitacion mostraba...'
(The inside of the room showed..)

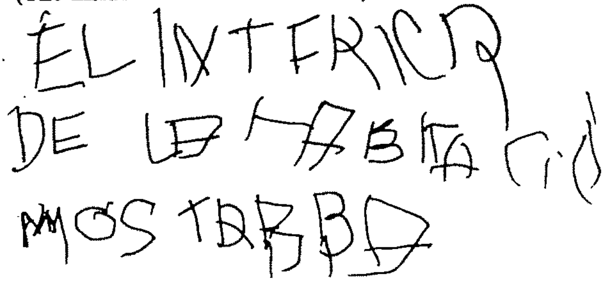


FIG. 9. *Case 3.* Right hand aphasic agraphia.

involved proximal and distal parts of the upper limb (e.g., throwing a ball) proximal movements proved to be more accurate, and in every instance the examiner could discern that the patient was trying to make the appropriate movement. Although on imitation and with the actual object, performance improved, he still made many temporospatial errors. No apraxia was observed in facial or whole-body movements. Case 3 also showed temporospatial errors on command, imitation and with use of actual objects when using the right upper limb.

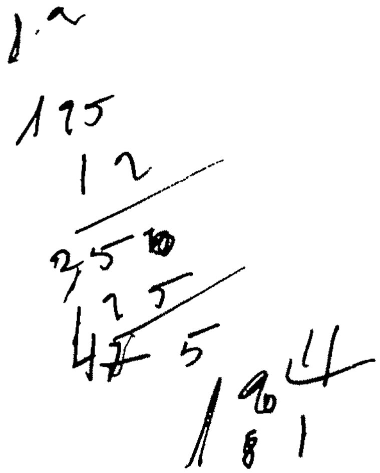


FIG. 10. *Case 1*. Spatial dyscalculia.

Dissociative phenomena. These were clearly present in Cases 1 and 3. Case 1 showed uncooperative and oppositional movements with the left hand, such as putting his glasses on his nose with the right hand and removing them with the left. During examination of Case 3, involuntary and antagonistic behaviour of his left hand was clearly observed (e.g., while the patient was trying to open a case with his right hand, the left prevented him). Although less frequent, some involuntary and oppositional movements of the right hand were also seen without the patient being conscious of this fact (e.g., when asked to write with his left hand, his right one took the sheet of paper and dropped it to the floor; when asked why he had done that, he denied having performed such an act).

Follow-up. Case 2 was reevaluated 3 months after the operation. He had full recovery of callosal functions without any clinical evidence of interhemispheric disconnection. A control CT scan showed a small hypodense lesion involving the dorsocaudal portion of the genu and the rostral third of the body of the callosum with minimal involvement of the anterior left cingulate gyri with no further evidence of extracallosal damage (fig. 11).

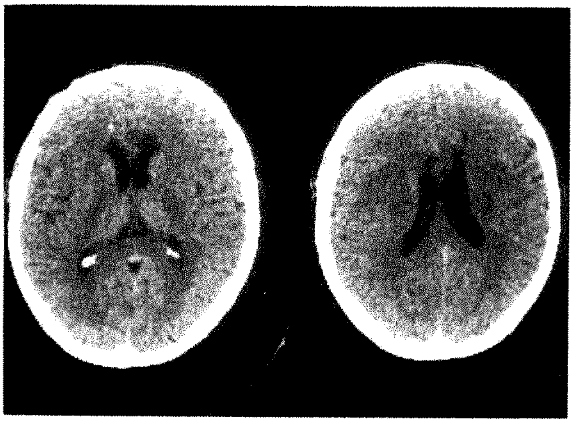


FIG. 11. *Case 2.* Unenhanced CT scan 3 months after operation showing damage affecting the dorsal portion of the genu and the anterior part of the body of the corpus callosum; a small lesion is observed in the left anterior cingulate gyrus.

DISCUSSION

Three patients are presented who developed a partial interhemispheric disconnection syndrome as the main neurological manifestation of an anterior callosal haemorrhage secondary to rupture of a saccular aneurysm. We will now examine the clinical features relevant to the extracallosal damage, the presence of atypical lateralization of neuropsychological functions, the interhemispheric disconnection signs and their association with the specific portion of the corpus callosum involved by the lesion, and new aspects of the pathogenesis of callosal haemorrhages secondary to ruptured aneurysms.

Clinical features of extracallosal damage

All 3 patients presented abnormal neurological findings such as mild corticospinal signs in the lower limbs, abnormal reflexes, tactile extinction and urinary incontinence. These 'extracallosal' signs may result from pressure of the haemorrhage on the descending precentral and frontal fibres producing the corticospinal signs and the grasp reflex (Fisher, 1982) and on the anterior cingulate gyrus and adjacent frontal regions producing tactile extinction and urinary incontinence (Andrew *et al.*, 1966; Heilman and Valenstein, 1972). Despite the fact that 2 out of our 3 patients (Cases 1, 2) had angiographic evidence of vasospasm, it seems most unlikely that an ischaemic lesion contributed to the development of the extracallosal symptomatology, since none of the patients presented features commonly seen with ischaemia in the territory of the anterior cerebral artery, such as persistent disturbances of consciousness, amnesia, confabulation, personality and psychiatric disorders, eye movement abnormalities, hypometria, bradykinesia, catatonia, neglect and aphasia (Critchley, 1930; Alexander and Freedman, 1984; Eslinger and Damasio, 1984; Brust, 1986; Meador *et al.*, 1986). CT studies likewise failed to reveal ischaemic changes in the anatomical regions surrounding the corpus callosum.

At the onset, all 3 patients showed similar speech difficulties, characterized by paucity of speech, long latencies and hypophonic but normally articulated verbal output. Transient mutism is a common finding after complete commissurotomy (Bogen, 1985) and during the recovery period, speech production is limited to a few short grammatically correct and well articulated sentences. Although these speech disturbances may be attributed to damage in the anterior cingulate gyrus, they may also reflect callosal dysfunction (Sussman *et al.*, 1983), since electrical stimulation of the genu may produce inhibitory effects on speech output (Schaltenbrand *et al.*, 1972).

Lateralization of cognitive functions

Case 1 developed the typical clinical manifestations of anterior interhemispheric disconnection observed in right-handed patients with left hemisphere dominance for language and praxis (i.e., agraphia, tactile anomia and ideomotor apraxia for the left hand; Bogen, 1985). On the other hand, Cases 2 and 3 presented with an atypical lateralization pattern of neuropsychological function and, in both, CT scan measurements of the occipital and frontal 'petalias' lend support to such an atypical cerebral dominance pattern.

The lateralization of the disconnection signs in our ambidextrous patient (Case 2) suggests that his right hemisphere was dominant for writing (he had a right hand agraphia) whereas the left hemisphere was dominant for visuospatial skills (he had difficulties in copying with the left hand). Similar cases of atypical lateralization of neuropsychological functions in patients with the callosal disconnection syndrome are not unknown. The left-handed patients of Gazzaniga and Freedman (1973), Poncet *et al.* (1978) and Gur *et al.* (1984) behaved as right-handers with left hemisphere dominance for language and right hemisphere dominance for visuospatial skills, whereas the right-handed patient of Trescher and Ford (1937) developed disconnection signs compatible with right hemisphere dominance for language. Lastly, Schott *et al.* (1975) reported an ambidextrous patient with a callosal tumour who presented with right aphasic agraphia and tactile alexia, bilateral constructional apraxia and a partial left ear extinction on dichotic listening.

Our Case 3 showed right hemisphere dominance for language (he had a right hand agraphia), skilled motor movements (he had a right ideomotor apraxia) and visuospatial skills (he had difficulties in copying with the right hand), thus showing a hemisphere dissociation between dominance for handedness and dominance for language and praxis. A similar dissociation of handedness and praxis has been recently reported in right-handed patients with right hemisphere strokes (Rapcsak *et al.*, 1986; Berthier *et al.*, 1987) but to our knowledge, Case 3 is the first case of a right-handed person with a callosal disconnection syndrome and crossed lateralization of praxis, language and handedness.

Clinical features of interhemispheric disconnection

The most striking clinical features in our patients were due to interhemispheric disconnection and included disturbances of somaesthetic transfer, tactile anomia, agraphia, ideomotor apraxia, difficulties in copying, spatial dyscalculia and the 'alien hand' sign.

Disturbance of somaesthetic transfer

All 3 patients showed an impaired ability to cross-replicate hand postures and to cross-localize stimulation of finger tips, which constitute the hallmark of the interhemispheric disconnection syndrome (Bogen, 1985). In monkeys, the interconnecting callosal fibres responsible for the transfer of somaesthetic information are localized in the rostral portion of the caudal half of the callosal body (Pandya *et al.*, 1971). As the transfer of such information, whether proprioceptive, tactile or stereognostic, is not dependent on hemispheric dominance, dysfunction regularly occurs when the lesion affects that portion of the callosal body (Jeeves *et al.*, 1979; Bentin *et al.*, 1984). This region was involved by the haemorrhage throughout. However, damage was probably partial in Case 2, since the deficit in somaesthetic transfer reverted to normal and tactile naming was preserved.

Unilateral tactile anomia

This deficit is the result of the failure to transfer somaesthetic information across the callosum from the (nonverbal) nondominant hemisphere to the intact naming mechanism of the (verbal) dominant hemisphere. Brion and Jedynak (1975) proposed that unilateral tactile anomia is most frequent with callosal lesions extending from the splenium caudally to the junction of the anterior and medial portions of the callosal body rostrally. Tactile anomia was present in Cases 1 and 3, both with extensive damage in the callosal body but without involvement of the splenium. It was absent in Case 2, in whom the caudal third of the callosal body was not involved by the haemorrhage. Therefore, fibres transferring this complex somaesthetic information may be primarily located in the most caudal part of the callosal body, posterior to those transmitting other somaesthetic modalities. In support, Degos *et al.* (1987) reported the case of a patient with posterior callosal infarction who had tactile anomia but partially preserved somaesthetic transfer for other modalities.

Unilateral agraphia

Apraxic and aphasic agraphia of the nondominant hand have been reported in patients with callosal lesions (Bogen, 1969; Watson and Heilman, 1983; Roeltgen, 1985) and it was speculated that the type of unilateral agraphia may be related to lesions of a specific part of the corpus callosum (Watson and Heilman, 1983).

The cases described by Sweet (1945) and Watson and Heilman (1983), as well as our Case 1, are examples of apraxic agraphia of the left (nondominant) hand. In all of them, the lesion involved the callosal body, sparing most of the genu and splenium. Unilateral apraxic agraphia may therefore be due to interference of transcallosal transmission of graphomotor engrams from the (verbal) dominant parietal lobe to the nondominant hemisphere through the body of the callosum.

Aphasic agraphia, on the other hand, has been described in patients with callosal lesions of variable extent and location. Thus in some patients (as in our Case 3) the lesion roughly involved the anterior four-fifths of the corpus callosum (Liepmann and Mass, 1907; Geschwind and Kaplan, 1962; Yamadori *et al.*, 1980; Goldenberg *et al.*, 1985; Graff-Radford *et al.*, 1987) while in our Case 2, as well as Case D in Brion and Jedynak (1975), it spared the splenium, most of the genu and the caudal third of the callosal body. Alternatively, aphasic agraphia has also been correlated with callosal lesions involving the caudal portion of the body and the splenium (Brion and Jedynak, 1975, Case D; Gersh and Damasio, 1981; Yamadori *et al.*, 1983; Degos *et al.*, 1987). As illustrated by our patients, the anterior form of aphasic agraphia can coexist with ideomotor apraxia (Case 3) or be dissociated from it (Case 2), depending on how posteriorly the callosal lesion extends. In contrast, the posterior form is rarely accompanied by apraxia but usually presents with clinical findings resulting from the disruption of the interhemispheric transfer of visual information such as double hemianopia, hemialexia and unilateral visual naming defects (Bogen, 1985).

Unilateral ideomotor apraxia

Apraxia of the nondominant limb in patients with callosal lesions may have different characteristics. Similar to the patients reported by Liepmann and Mass (1907), Sweet (1945), Klein and Ingram (1958), Schott *et al.* (1969), Barbizet *et al.* (1978), Watson and Heilman (1983) and Goldenberg *et al.* (1985), our Cases 1 and 3 had an ideomotor type of apraxia, since they could not use their hand on command, on imitation or while holding an object. As some of these previously reported cases also had extensive hemisphere damage, it was speculated that the extracallosal lesions, particularly in the supplementary motor area, may be important for the production of apraxia (Gazzaniga *et al.*, 1967; Goldenberg *et al.*, 1985). In our Cases 1 and 3, however, as well as in those described by Sweet (1945), Watson and Heilman (1983) and Graff-Radford *et al.* (1987), the lesion was restricted to the callosum, supporting the hypothesis that unilateral ideomotor apraxia may be primarily the result of disconnection of the area containing the visuokinaesthetic motor engrams in the dominant from the nondominant hemisphere (Liepmann and Mass, 1907) by a lesion restricted to the callosal body through which these engrams are presumably transmitted (Watson and Heilman, 1983). Like Case D in Brion and Jedynak (1975), our Case 2 failed to develop unilateral apraxia of the nondominant limb despite a callosal haemorrhage. It is possible that these patients had bilateral representation of visuokinaesthetic motor engrams, as well as verbal comprehension abilities in their nondominant hemisphere (Heilman and Gonzalez Rothi, 1985). Alternatively, callosal damage may not have been extensive enough to interrupt the fibres responsible for the interhemispheric transmission of these engrams.

Unilateral copying difficulty and dyscalculia

Our 3 patients had difficulty in copying drawings with the hand ipsilateral to their 'minor' hemisphere; in addition, Case 1 had such a severe spatial dyscalculia as to interfere with solving written arithmetic problems. The appearance of certain disorders of visuospatial function in our patients are evidence of the callosal impairment in the transfer of information from the minor nonlanguage dominant hemisphere to the dominant one, in keeping with previous reports (Bogen, 1969; LeDoux *et al.*, 1978). The clinicopathological study of Degos *et al.* (1987) has demonstrated that at least part of the interhemispheric parietal connection responsible for the transfer of some visuospatial functions travel through the caudal part of the callosal body and splenium. Since the splenium was intact in our patients, as well as in the patient of Graff-Radford *et al.* (1987), we may assume that these fibres in man course through the posterior half of the callosal body in agreement with the findings of Pandya *et al.* (1971) in nonhuman primates.

Dissociative phenomena

Other relevant clinical findings in our Cases 1 and 3 were the presence of intermanual conflict and the 'alien hand' sign. Brion and Jedynak (1972, 1975) described the presence of the alien hand sign in 6 patients with callosal disconnection syndrome and found that the damge invariably involved the cllosum from the splenium caudally to the middle of the body rostrally. This portion of the callosum was also damaged in our Case 1 and 3, as well as in the cases reported by Watson and Heilman (1983) and Graff-Radford *et al.* (1987). On the other hand, this portion of the callosum was partially spared in our Case 2, and in Case D described by Brion and Jedynak (1975), who also failed to show the alien hand sign.

The alien hand sign has also been observed in patients with hemisphere lesions, either in the medial frontal cortex (Goldberg *et al.*, 1981; Watson *et al.*, 1986; Magnani *et al.*, 1987) or in the posterior cerebral artery territory, sparing the callosum (Levine and Rinn, 1986). One difference between the 'callosal' and the 'hemisphere' types of alien hand sign is that in patients with the callosal type, the alien hand sign appears in the hand ipsilateral to the language and motor-dominant hemisphere, whereas in the hemisphere type, the alien hand sign develops in the hand contralateral to the lesion, regardless of the pattern of cerebral dominance.

Pathogenesis of callosal haemorrhages secondary to ruptured aneurysms

Crompton (1962) suggested that the direct jet from the ruptured anterior communicating artery aneurysm or the secondary dissection of an interfrontal subarachnoid haematoma would cause the blood to pass beneath the rostral callosal fibres and progress upwards into the septum pellucidum producing a septal or caval haematoma. From here, the blood may progress into the lateral ventricle or, more rarely, into the callosum. Less frequently, blood may pass over the dorsum of the callosum, producing a supracallosal or intercingulate subarachnoid haematoma which may then burst laterally into the parietal white matter or down into the callosum. None of these mechanisms, however, can explain the development of the callosal haemorrhage in our Case 3, since the CT scan showed neither a septal nor a supracallosal or intercingulate haematoma. We believe that this patient developed a small interfrontal subcallosal haematoma as a result of the first bleeding and by the time of the second bleed, this haematoma may have partially resolved, leaving subarachnoid adhesions which may have provided a route through which the jet of blood reached the callosal genu. A similar mechanism may apply to Sweet's case (1945) in which a saccular aneurysm located below the callosal rostrum (in the proximal portion of the anterior cerebral artery) was surrounded by coagulated blood and projected upwards into the substance of the callosum. Whatever the mechanism may be, it would be rather exceptional, since callosal haematomas after the rupture of anterior communicating artery aneurysms have invariably presented in association with haemorrhages in other locations (Crompton, 1962; Yock and Larson, 1980) and not as a single lesion as in our Case 3.

Bleeding from a pericallosal aneurysm may initially cause an intercingulate haematoma which later ruptures downwards into the callosum (Crompton, 1962). Alternatively, the callosal haematoma may be produced by the direct rupture of the aneurysm into the callosal substance since neither in our Cases 1 and 2 nor in those reported by Brion and Jedynak (1975) (Case D) and Graff-Radford *et al.* (1987) was there any evidence of extracallosal haemorrhage. Two anatomical features may readily account for the direct bleeding of a pericallosal aneurysm into the callosum: (1) these aneurysms are usually located at the pericallosal bifurcation above the genu, where the pericallosal artery often makes a sharp bend (Laitinen and Snellman, 1960) and (2) these aneurysms are closely attached to the callosal surface, where there is no subarachnoid cistern into which they can bleed (Mann *et al.*, 1984).

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DIFFERENTIATION OF TYPICAL ABSENCE SEIZURES IN EPILEPTIC SYNDROMES

A VIDEO EEG STUDY OF 224 SEIZURES IN 20 PATIENTS

by C. P. PANAYIOTOPOULOS, T. OBEID *and* G. WAHEED

(*From the Division of Neurology, King Khalid University Hospital, Riyadh, Saudi Arabia*)

SUMMARY

This is a comparative video-electroencephalographic (EEG) study of typical absence seizures in 4 epileptic syndromes. In 20 patients, 224 absences were recorded and analysed. Significant clinical and EEG differences were found in the seizure patterns of childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy with absences (JMEA) and myoclonic absence epilepsy (MAE). Clinically, CAE demonstrated more severe impairment of consciousness than JAE while, in JMEA, ictal manifestations were frequently mild and difficult to detect. In the latter, the adolescent patient usually continued his activity, was able to perform even mathematical calculations and often his speech was not disturbed. In children with JMEA, impairment of consciousness was more apparent and sometimes severe. Automatisms occurred in all 4 epileptic syndromes and were proportional to the severity of the demonstrated impairment of consciousness, being rare in JMEA but frequent in CAE and JAE. Expressive speech and overbreathing usually persisted for 1–2 s after the onset of the EEG ictal discharge in CAE. It was less disturbed in JAE where in some absence seizures, interrupted speech and overbreathing were restored during the ictus. A characteristic clinical manifestation of CAE was opening of the eyes in all absence seizures within 1.8±0.6 s (max. 2.5 s) from the onset of the EEG paroxysms. This early eye-opening behaviour was not observed in JMEA. In MAE, rhythmical myoclonic jerks at 3 Hz make the diagnosis unmistakable. Myoclonic jerks were extremely rare in the absences of JMEA, although all patients had independent myoclonic jerks on awakening.

The ictal EEG discharge was longer in JAE (mean 16.3±7.1 s) than in CAE (12.4±2.1 s) or JMEA (6.6±4.2 s). The opening phase of the EEG paroxysms did not show significant differences in CAE, JAE and JMEA but significant changes were found in their initial and terminal ictal phases. In JMEA, the spike-multiple spike-slow wave complexes were not rhythmic and frequently demonstrated variable spike-slow wave relationships. Ictal discharge fragmentations and spike-wave discharges looking like compressed capital Ws were often seen and are characteristic of JMEA.

seen and are characteristic of JMEA.

Absence seizures demonstrated a more severe impairment of expressive rather than receptive speech, irrespective of differences between syndromes. Evoked as well as spontaneous automatisms occurred in the same patients. Their eyes moved frequently in response to external stimuli, reflex blinking to visual threat was usually retained, even in CAE, and the same patient often had both simple and complex absences. The classification of automatisms can serve only descriptive purposes.

Correspondence to: Professor C. P. Panayiotopoulos, Department of Clinical Neurophysiology and Epilepsy, St. Thomas' Hospital, London SE1 7EH, UK.

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INTRODUCTION

'Typical absences' is the recommended term for generalized, predominantly nonconvulsive, seizures of children and young adolescents instead of the traditional 'petit mal' (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). They manifest with impairment of consciousness linked with 3 Hz spike and wave generalized electroencephalographic (EEG) discharges. Transient lapse of consciousness may be the only clinical manifestation (simple typical absences) or they may be associated with other minor clinical features such as tonic, clonic and atonic movements, automatisms and autonomic phenomena alone or in any combination (complex typical absences).

Typical absences are the only or most important seizure type in the three different idiopathic generalized epileptic syndromes: (1) childhood absence epilepsy (CAE); (2) juvenile absence epilepsy (JAE); and (3) juvenile myoclonic epilepsy with absences (JMEA) (Commission of ILAE, 1985).

CAE is the best known syndrome of absence epilepsy. Simple and/or complex attacks start between 4 and 8 yrs of age, are frequent, hence the term 'pyknolepsy'. Simple absences may be accompanied by upward deviation of the eyes and complex absences by motor phenomena such as retropulsion of the head and trunk. Generalized tonic-clonic seizures (GTCS) develop in 30–40% of the cases in adolescence, usually after an average of 6 yrs from onset of the disease (Loiseau *et al.*, 1983; Commission of ILAE, 1985). The EEG discharge is 2.5–3.5 Hz spike and wave.

JAE occurs around puberty. 'The absences are the same as in CAE but retropulsive movements are less common. Seizure frequency is lower than in CAE. GTCS are common, occur mainly on awakening and may precede the appearance of absences. The patients may also have myoclonic jerks. The prognosis is still unclear. The spike-wave discharge is often faster than 3 Hz' (Commission of ILAE, 1985).

JME is an epileptic syndrome of the second decade of life with a peak at 15 yrs of age (Janz, 1969, 1985; Delgado-Escueta and Enrile-Bacsal, 1984; Commission of ILAE, 1985; Obeid and Panayiotopoulos, 1988). It is frequently unrecognized and misdiagnosed. The salient clinical manifestations consist of myoclonic jerks mainly on awakening and GTCS precipitated by sleep deprivation. Absences are an inconspicuous feature of the syndrome which have attracted little interest despite their occurrence in 10–37% of the patients with JME. They are described as simple absences with 3–4 Hz spike-wave discharges. Remission of the seizures is uncommon. An autosomal recessive mode of inheritance for JMEA has been demonstrated recently (Panayiotopoulos and Obeid, 1989).

Despite the above and other significant syndrome differences, the absence seizures manifested in all three epileptic syndromes are described as uniform and stereotyped, that is typical absences, simple, or complex, with 3–4 Hz spike-slow wave discharges. Some minor quantitative differences regarding duration (longer in CAE), frequency (hundreds per day in CAE-pyknolepsy) and retropulsion/conjugate eye movement (less frequent in JAE) are reported (Commission of ILAE, 1985). These are not sufficient to differentiate absence seizures in the epileptic syndromes. Furthermore, the studies of absences in JMEA are limited; they are described as simple absence seizures with a 3.5–6 Hz spike-wave discharge (Janz, 1969, 1985; Delgado-Escueta and Enrile-Bacsal, 1984).

Additionally, absence seizures are related to another three epileptic conditions described recently. These are: (1) myoclonic absence epilepsy (MAE) (Tassinari and Bureau, 1985); (2) eyelid myoclonus with absence seizures (Jeavons, 1982; Panayiotopoulos, 1987); and (3) circling epilepsy with absences (Gastaut *et al.*, 1986).

The lack of differentiating clinical and EEG features in typical absence seizures is apparent both in classical and more recent studies where absences are studied in a unitary fashion (Holmes *et al.*, 1987). The results and conclusions drawn from these studies are bound to be skewed by the erroneous inclusion of cases of one epileptic syndrome, for example, JMEA in the study of another, such as CAE. The consequences of this for prognosis and genetic analysis are only too clear.

We have described recently the clinical EEG characteristics of 19 patients with JMEA and indicated that typical absences in JMEA may be different from those in other epileptic syndromes (Panayiotopoulos *et al.*, 1989). This study compares typical absence seizures in CAE, JAE, MAE, and JMEA. It shows that there are significant clinical and EEG differences which makes their distinction possible.

PATIENTS AND METHODS

Patients

The age and sex of the patients studied in each of the four epileptic syndromes considered are detailed in Table 1. There were 6 patients with CAE, 3 with JAE, 10 with JMEA and 1 with MAE.

TABLE 1. AGE AND SEX OF PATIENTS IN THE 4 EPILEPTIC SYNDROMES

	CAE			*JAE*			*JMEA*			*MAE*	
	Sex	*Age (yrs)*		*Sex*	*Age (yrs)*		*Sex*	*Age (yrs)*		*Sex*	*Age (yrs)*
1	F	9	1	M	18	1	M	8	1	M	11
2	M	5	2	M	18	2	M	17			
3	F	5	3	F	14	3	M	19			
4	F	8				4	M	21			
5	M	8				5	M	14			
6	F	7				6	F	16			
						7	F	20			
						8	F	17			
						9	F	22			
						10	F	14			

A firm clinical diagnosis was based on detailed family and patient history, neurological examination and video-EEG analysis. Patients with JMEA have long follow-up and family records as part of a prospective study on JME which was started 3 yrs ago and continues to date.

Video-EEG recordings

Video-EEG studies were made in all patients using a Telefactor-Modac 1 which allows simultaneous read-out of the EEG waveforms directly from the patient synchronously with the television signals-pictures of the patient. The data were monitored through a television screen and stored on video tapes for review. Sixteen channels were used with a longitudinal montage (fig. 1). Each patient's recording lasted from 3 to 7 h and was always attended by 2 of us to make necessary adjustments so as to achieve a better evaluation of the patient's state of awareness, responsiveness and level of consciousness during the attack. Patients were lying, sitting and occasionally standing. The video camera was aligned in order to have a clear view of the patient's face and body, with additional recordings of selected close-up views. All patients were asked to count their breaths during at least 2 sessions of overbreathing (OB). This simple method allows easy, objective and unequivocal evaluation of the speech and mental functions involved in counting. Similarly, patients had long sessions of reciting from the Holy Qur'an which involves hyperventilation and the mental functions of reading, memory and recollection. In patients who ceased counting, OB or reciting because of an absence, the evaluation of their responsiveness, awareness and level of consciousness was made by delivering strong auditory stimuli such as calling their name, a hand clap, brief orders such as 'open your mouth', 'lift your hand' or pronouncing numbers. On a few occasions responsiveness was tested by sensory (passive movements of the limbs, tapping the skin) and visual (fast hand movement towards the eyes) stimuli. In other patients who continued their activities despite the EEG evidence of a seizure, a battery of more refined tests was delivered. The patients were asked to repeat numbers, make calculations, recite from the Holy Qur'an, and say the date. The responses and the speed of response were compared with similar ones delivered during normal EEG activity. All patients had at least one absence seizure with the eyes open in the preictal phase but, in the majority, the eyes were closed preictally. There was a minimum of 7 sessions with a 3 min OB in all records. Each patient had at least 4 seizures recorded.

ANALYSIS OF DATA

Video-EEG recordings

These were reviewed by all of us in sessions where the clinical and previous EEG data of the patient were also reevaluated. Each seizure was viewed repeatedly and each observer made his own comments which were discussed by all of us until a consensus was reached. The preictal state of the patient was recorded as part of the final evaluation (eyes open or closed, lying or sitting, overbreathing or talking, counting or reciting, relaxed or moving). All movements and the responses of the patient during the attack were timed and graphed in relation to the onset of the EEG discharge and stimuli given to the patient. The EEG discharges were evaluated for duration, frequency and morphology of their complexes. The EEG frequency of the spike-wave complexes were measured in the first (opening phase), the following 3 s (initial phase) and the last 3 s (terminal phase). In nonrhythmic discharges the number of complexes in a given ictal phase were counted and this was divided by the number of seconds of the phase. The measurements were made at optimum speed and amplitude magnifications which are provided by the video-EEG machine. Particular attention was paid to the continuity of the whole discharge (*see* below for fragmentations). The average time required for the evaluation of a seizure was 1 h.

Student's t test was used for statistical evaluation. Values are expressed as mean ±SD.

RESULTS

Childhood absence epilepsy

Forty-six (mean for each patient 5±2) absence seizures were recorded; 42 (mean 5±2) of them occurred during OB, 28 (mean 3±2) during counting while hyperventilating and 40 (mean 4±2) with eyes closed. In all of the 46 absences, consciousness was severely disturbed (Table 2). There was no occasion when the child would respond to any of the stimuli administered during the discharge although reflex response to visual threat by blinking or to pain by withdrawal was usually retained. There was no recollection of ictal events except on a few occasions when a slap on the legs, a clap or a number given 1–2 s before termination of the

TABLE 2. ICTAL CLINICAL MANIFESTATIONS

	*CAE**	*JAE**	*JMEA**
Impairment of consciousness	46/46	49/50	20/108
Eyes opened	40/40	20/39	4/68
Counting ceased	28/28	31/32	6/30
OB ceased	42/42	34/42	5/90
Blinking at 3 Hz	4/46	0/50	0/108
Irregular blinking	18/46	3/50	4/108
Eyes moved	30/46	25/31	39/44
Automatisms	36/46	37/50	4/108
Response to commands	0/30	12/50	103/108
Evoked automatisms	7/10	8/12	1/40
Reflex responses to visual threat	6/12	7/7	30/30
Verbal responses	0/30	7/30	50/52
Recollection of ictal events	5/46	15/50	105/108

* No. of observations or positive response/number of trials.

TABLE 3. LATENCY OF ICTAL EYE-OPENING, CESSATION OF OB AND COUNTING

	CAE	*JAE*	*JMEA*
Eyes opened (no./trial)	40/40	20/39	4/68
Mean (s)	1.8	7.0	
STD (s)	0.6	4.0	
Max (s)	2.5	17.0	
Min (s)	1.0	4.0	
OB stopped (no./trial)	42/42	34/42	5/90
Mean (s)	1.4	3.0	
STD (s)	0.5	3.0	
Max (s)	2.0	10.0	
Min (s)	0.0	1.0	
Counting stopped (no./trial)	28/28	31/32	6/30
Mean (s)	1.5	2.8	
STD (s)	0.4	2.3	
Max (s)	2.0	6.0	
Min (s)	0.0	1.0	

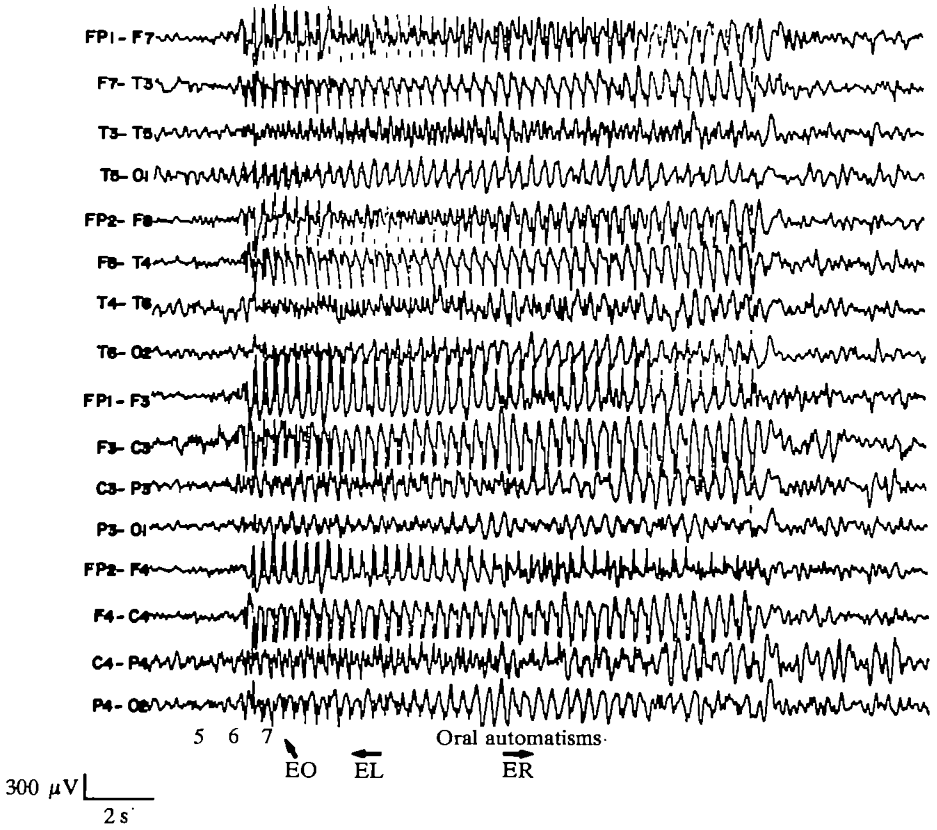


FIG. 1. Video-EEG recording of a typical absence seizure from an 8-yr-old girl with childhood absence epilepsy (pyknolepsy). She was counting her breaths preictally. Her eyes were closed. Overbreathing and counting ceased within 2 s of the onset of the EEG paroxysm. Note that she was able to count correctly the next sequential number 7 although the attack had started. Her eyes opened and moved to the directions indicated by the arrows. Oral automatisms, mute-counting, were observed 5 s after the onset of the attack. The EEG discharge is rhythmic with gradual slowing from the opening to the terminal phase. EO = eyes opened; EL = eyes moved to the left; ER = eyes moved to the right.

attack would be remembered. Twice a child performed postictally a task given to him just before the end of the ictus. OB ceased invariably within 0–2 s (mean 1.4±0.5), counting 0–2 s (1.5±0.4) and eyes opened 1.0–2.5 s (mean 1.8±0.6) after the onset of the EEG discharge (Table 3). Regular eye-blinking at 3 Hz occurred in 4 seizures only. In another 18 absences irregular 1–3 Hz blinking occurred usually in clusters of 1–4 s. The eyes remained still in only 16 seizures and in the remaining 30, eyes would move slowly and change direction (fig. 1). The eye movements were usually slow and directed towards strong external stimuli such as calling the name of the patient or a loud noise. Upward deviations of the eyes were observed in 6 seizures only. Neither eye blinking nor upward deviations were observed regularly in the same patient. Automatisms occurred in all 6 children in 36 seizures. The most common were oral automatisms which appeared 3 to 6 s after the onset of the discharge and were similar to the counting (mute counting) or OB movements of the mouth. More complex automatisms such as fumbling with the clothes occurred in 2 children and these were clearly related to the preictal posture and movements of the patient. None of the automatisms was stereotyped in any of them. In addition, 2 seizures were observed where hand or leg automatisms were not preceded by ones involving the face. Four children in 10 absences did not have automatisms. Evoked automatisms of the lower limbs occurred in a child after placing a pen between the big and second toes. In another patient, the automatisms were modified by asking him to hold an object. The new automatisms consisted of fumbling with the object. Clonic movements of the head and hands of small amplitude occurred in 3 out of 5 absences in 1 patient. Postictal confusion was not apparent in any instance.

Juvenile absence epilepsy

Fifty (mean for each patient 17 ± 4) absence seizures were recorded; 42 (mean 14±3) occurred during OB, 32 (mean 11±2) while counting their breaths and 39 (mean 13±4) with eyes closed. Consciousness was disturbed in all but 1 absence seizure (Table 2). This was a 3 s duration discharge during which the patient stopped counting momentarily but remembered a simple mathematical exercise given to him during the attack and replied correctly with no hesitation postictally. In all other seizures, the pattern of the impairment of consciousness was similar (figs 2, 3). Awareness, perception, responsiveness, memory and recollection were impaired with marked variation in severity from seizure to seizure even in the same patient but was not as severe as in CAE. Every patient in 2 seizures each responded to his name with 'aaa?' or 'yes' and, in 1 seizure, a patient answered correctly the question 'What is you name?' (fig. 2). The earliest time of obtaining these verbal responses was 9–17 s from the onset, 2–10 s before termination. In all other seizures, questions and stimuli elicited no verbal response. In 12 seizures and in all patients, the eyes would open at command and follow the examiner from as soon as 3 s after the onset (fig. 2). All patients had at least 1 seizure in which they would be able to recall ictal events such as a number or a phrase given to them 5–8 s before the cessation of the discharge. On one occasion, a patient remembered a slap on her leg a 5 s after the onset of a 17 s duration discharge. She could also recall 2 out of 3 numbers given to her subsequently. OB ceased in 34 (11±2) out of the 42 seizures within 1–10 s (mean 3±3) from the onset (Table 2). Eyes opened spontaneously in 20 (7±3) out of the 39 trials within 4–17 s from the onset, never before 4 s (Table 2). On 3 occasions there was irregular blinking in 2 patients. Eyes moved in response to external stimuli in all patients but not in all seizures. Counting stopped in all but 1 of the 32 (11±2) trials within 1–6 s from the onset. However, counting was slowed with mistakes in the sequence but not the pronunciation of the numbers when maintained for more than 2 s from the onset.

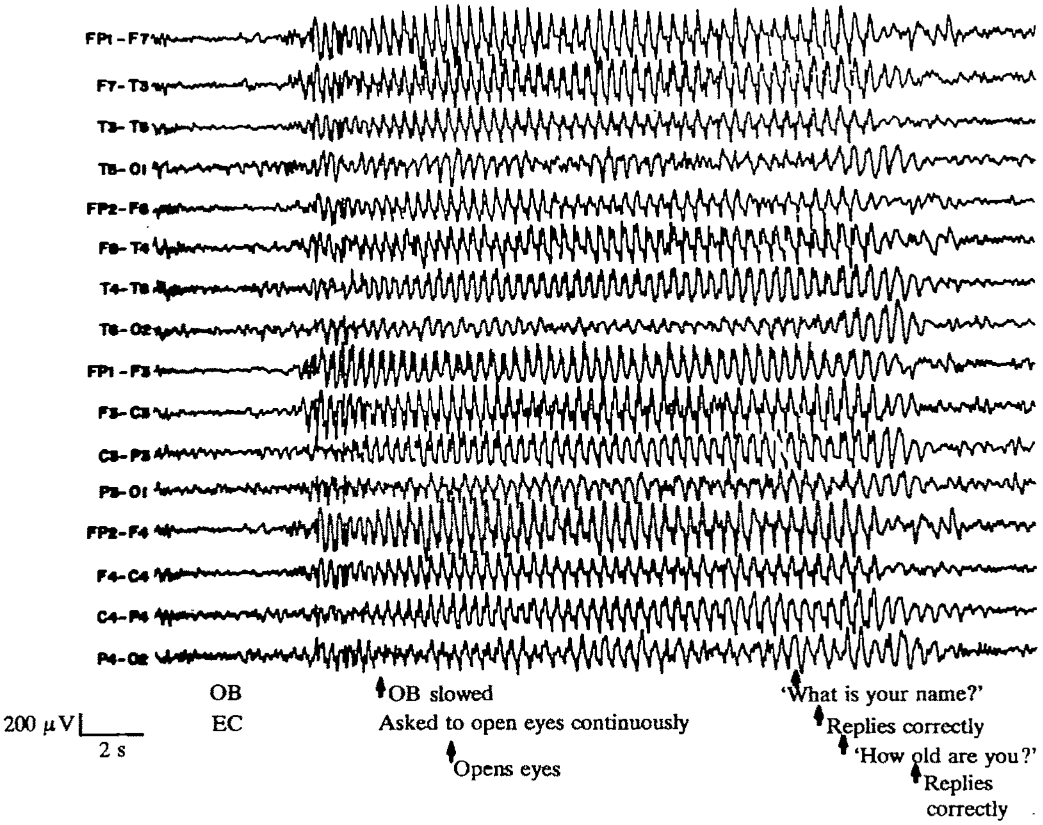


FIG. 2. Video-EEG recording of a typical absence seizure from a 14-yr-old girl with juvenile absence epilepsy. She was overbreathing with eyes closed in the preictal phase. She opened her eyes after many instructions and was encouraged to keep them open despite her tendency to close them. She correctly said her name, in response to a relevant question 5 s before termination of the discharge (arrows). Also, she replied immediately and appropriately to the question 'What is your age?' which was administered before the end of the attack. Overbreathing slowed in depth and rate but continued throughout the attack. Note the regularity of the EEG discharge and the gradual slowing from onset to termination. OB = overbreathing; EC = eyes closed.

On a few occasions the patients would utter one or more numbers out of sequence during the attack. A similar situation was observed during recitation from the Holy Qur'an which slowed, with repetitions of the same word or impairment of sequences when continued after 2 s from the onset. There were no mistakes in pronunciation. OB, counting or recitation were resumed during the attack on 6 occasions (fig. 3). Automatisms occurred in 37 (12 ± 5) out of the 50 seizures (Table 2). Oral automatisms were the most common and were similar to mute counting or OB. Automatisms of the upper and lower extremities without preceding ones in the face, as well as evoked automatism, were observed in all patients. Automatisms, usually simple movements, were often a reproduction of preictal habitual movements. Evoked automatisms were elicited in all patients. There was only 1 absence seizure with a prolonged automatism involving scratching of the genitalia. Automatisms would appear any time during the ictus from 1–17 s after the onset. There was no apparent postictal confusion.

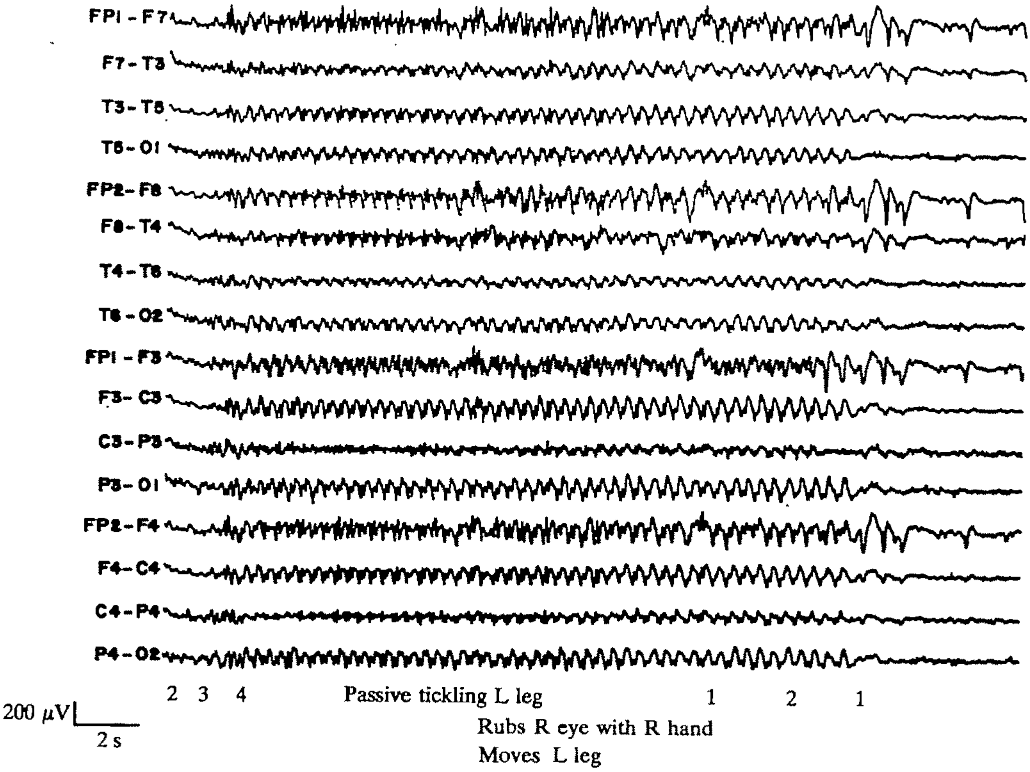


FIG. 3. Video-EEG recording of a typical absence seizure from an 18-yr-old male patient. Counting (numbers) discontinued at the initial phase but was resumed, in wrong sequence, 5 s before termination. Evoked automatisms from left leg and spontaneous, de novo, automatisms from right hand occurred simultaneously without preceding orofacial ones. The EEG showed multiple-spike slow wave complexes (*see* text) but the regularity of the discharge is apparent.

Juvenile myoclonic epilepsy with absences

EEG paroxysms of more than 3 s were recorded on 108 occasions. In 6 patients, no clinically discernible changes were observed (fig. 4). The previous activity of the patient was not interrupted or changed in any way. The performance in simple arithmetical calculations, reading, repeating numbers or phrases and reciting from the Holy Qur'an was considered satisfactory both during the recording and on replays by 3–5 evaluators. In addition, none of the patients admitted subjective changes during the discharges.

In 3 out of the 4 patients with clinical manifestations, these were subtle and could easily have escaped notice if specific tests were not given (Table 3). One patient had 3 episodes in which minor clinical manifestations would be demonstrated; 2 occurred during recitation from the Holy Qur'an. There was a brief speech hesitation or discontinuation with some stuttering (fig. 5). He would resume recitation, repeating the last phrase 0.5–1 s before termination of another 6 s

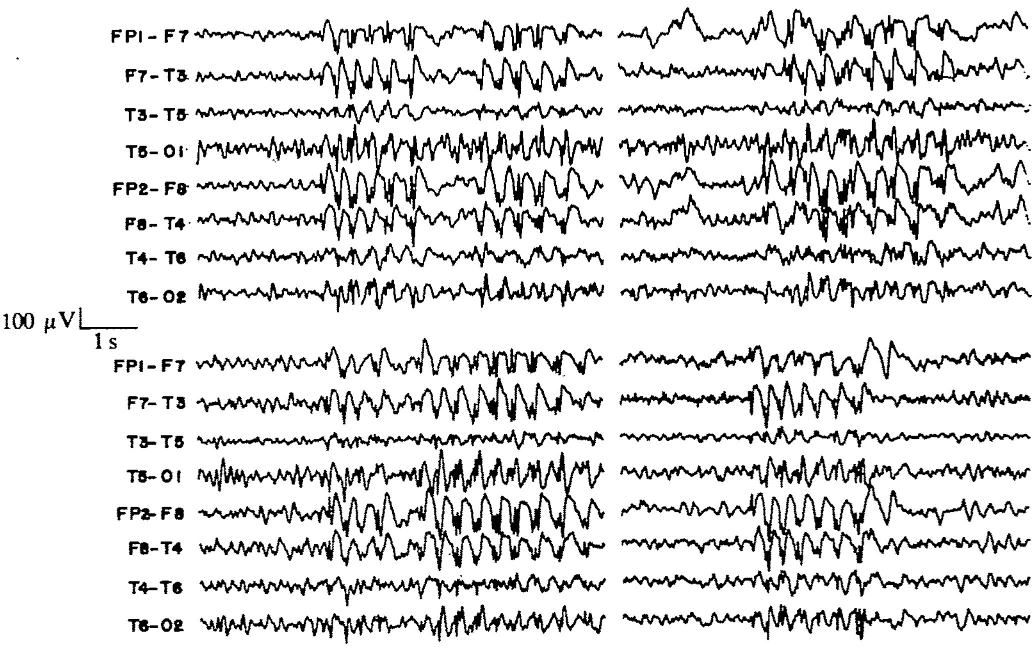


FIG. 4. Video-EEG recording of typical absence paroxysms from a 19-yr-old male patient with JMEA. There were no overt clinical manifestations. Note discharge fragmentations, irregularities of rhythm and spike or multiple spike-slow wave relations (*see* text).

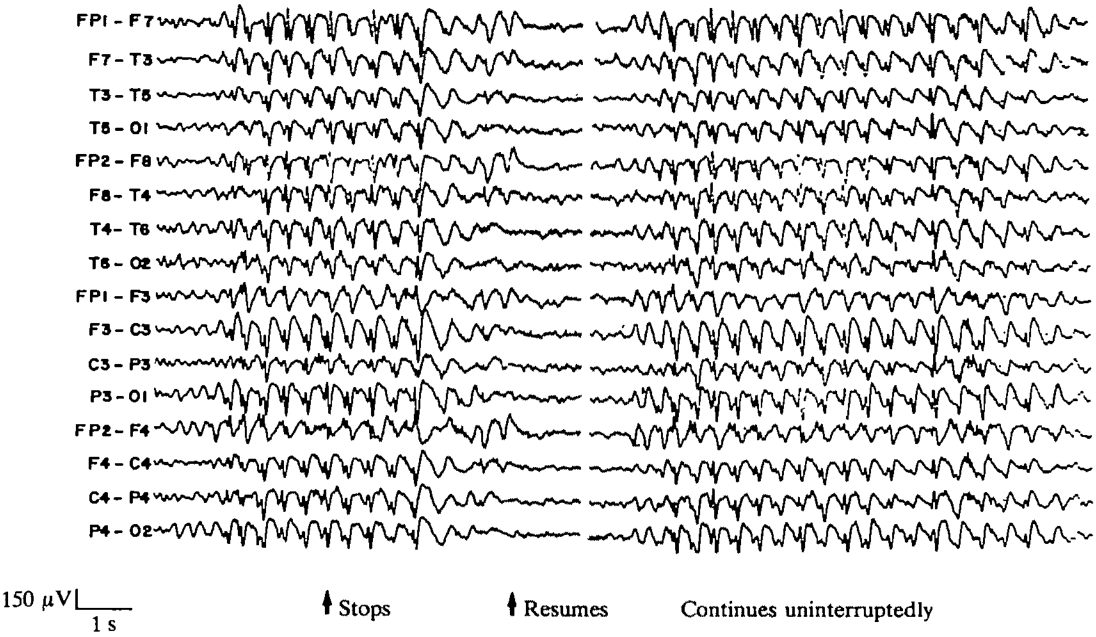
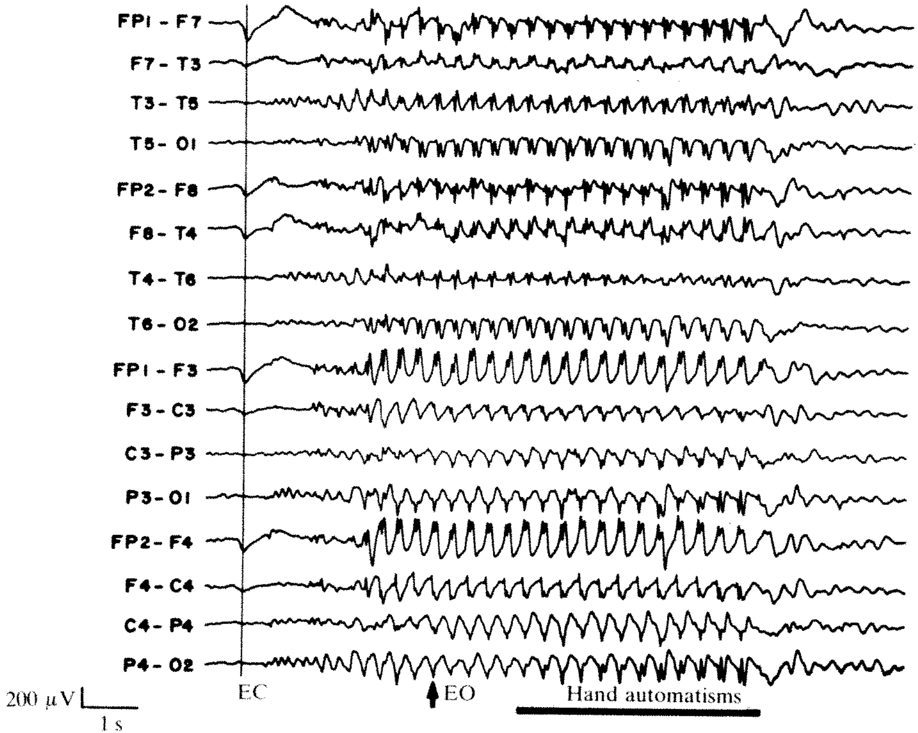


FIG. 5. Video-EEG recording of 2 typical absence seizures from a 17-yr-old male patient with JMEA. He is sitting in the praying position and reciting from the Holy Qur'an. He stops, stutters and continues postictally in one of the absences (left) while no detectable clinical changes occurred in the other (right). The EEG discharges are exceptionally rhythmic for JME but abrupt and irregular variations in the amplitude of the spikes are apparent.

discharge. On another occasion, he would hesitate again, stop and miss one of a series of numbers during counting with OB. Similar changes were observed in another patient. A third patient would only slow down his responses to mathematical calculations. In all these 3 patients, similar discharges occurred with no perceptible clinical changes (figs 4, 5). Severe impairment of consciousness was observed only in a child who had simple and complex absence seizures. Myoclonic jerks did not occur during the absences except in this child who had rare single jerks either independently or in the attack of a few of his absences. Postictal confusion was not observed.

Myoclonic absence epilepsy

There were 20 absence seizures recorded, all precipitated by eye closure; that is, they appeared within 1–5 s after closing of the eyes (fig. 6). The patient would stop counting and OB simultaneously with the initiation of opening and deviation of the eyes upwards and to the left and rotation and clonic movements of the head to the left at 3 Hz. The onset of these clinical manifestations was between



Head turns to left with clonic movements at 3 Hz

FIG. 6. Video-EEG recording of a typical absence seizure from an 11-yr-old boy with myoclonic absence epilepsy. Note the rhythmicity and smooth slowing of the discharge and the constant spike-slow wave relations.

1.5–2 s after the beginning of the EEG discharge. There was severe impairment of consciousness, similar to that seen in CAE. The patient would only remember slapping of the leg or hand but not numbers or other phrases given during the ictus. Reflex responses to visual threat were retained. Automatisms consisted of habitual movements of the hands and fingers or the legs and toes 4–6 s after the onset of the EEG paroxysms (fig. 6). These were observed many times during the video-EEG recording without ictal discharges. No oral or other facial automatisms were observed. There was no postictal confusion.

TABLE 4. ELECTROENCEPHALOGRAPHIC FREQUENCY ANALYSIS OF ICTAL PAROXYSMS

		Ictal phase (Hz)			*Frequency difference (Hz)*		
	Duration (s)	*Opening (1st s)*	*Initial (2–4 s)*	*Terminal (last 3 s)*	*O–T*	*O–I*	*I–T*
Childhood absence epilepsy (n = 46)							
Avg	$12.4^{a,b}$	3.4	$3.0^{a,b}$	2.5^{b}	0.9^{b}	$0.4^{a,d}$	0.4^{b}
STD	2.1	0.3	0.2	0.2	0.2	0.2	0.1
Max	18.0	4.0	3.3	2.9	1.3	0.9	0.7
Min	9.0	3.0	2.7	2.3	0.5	0.2	0.3
Juvenile absence epilepsy (n = 50)							
Avg	16.3^{c}	3.5	2.9^{c}	2.5^{c}	1.0^{c}	0.6	0.4^{c}
STD	7.1	0.4	0.2	0.3	0.4	0.4	0.2
Max	29.0	4.3	3.2	3.0	1.9	1.3	0.9
Min	3.0	2.5	2.5	2.1	0.3	0.4	0.1
Juvenile myoclonic epilepsy with absences (n = 108)							
Avg	6.6	3.4	2.8	2.9	0.5	0.6	−0.1
STD	4.2	0.6	0.3	0.4	0.4	0.4	0.2
Max	18.0	4.5	3.5	3.5	1.3	1.5	0.3
Min	3.0	2.4	2.2	2.3	−0.1	−0.3	−0.8
Myoclonic absence epilepsy (n = 20)							
Avg	7.2	4.3	3.6	3.1	1.2	0.7	0.5
STD	1.4	0.3	0.1	0.3	0.5	0.3	0.3
Max	10.0	5.0	3.7	3.2	2.4	1.4	1.5
Min	4.0	4.0	3.5	2.1	0.8	0.4	0.4

O = opening, I = initial, and T = terminal ictal phase. Statistically significant differences are indicated: ^{a} = $P < 0.02$ CAE vs JAE, ^{b} = $P < 0.001$ CAE vs JMEA, ^{c} = $P < 0.001$ JAE vs JMEA, ^{d} = $P < 0.01$ CAE vs JAE.

Electroencephalographic findings

Table 4 shows the analysis of the ictal discharge frequency. No significant differences were found in the frequency of the opening phase, while both the initial and terminal phases of JMEA were significantly different than in CAE and JAE ($P < 0.001$). A 0.4–0.6 Hz slowing of the discharge from the first to the following 3 s of the attack was found in all the 4 absence syndromes. A further 0.4 Hz slowing occurred from the initial to the terminal phase in CAE and JAE but not in JMEA ($P < 0.001$). The duration of the discharges is longer in JAE and shorter in JMEA.

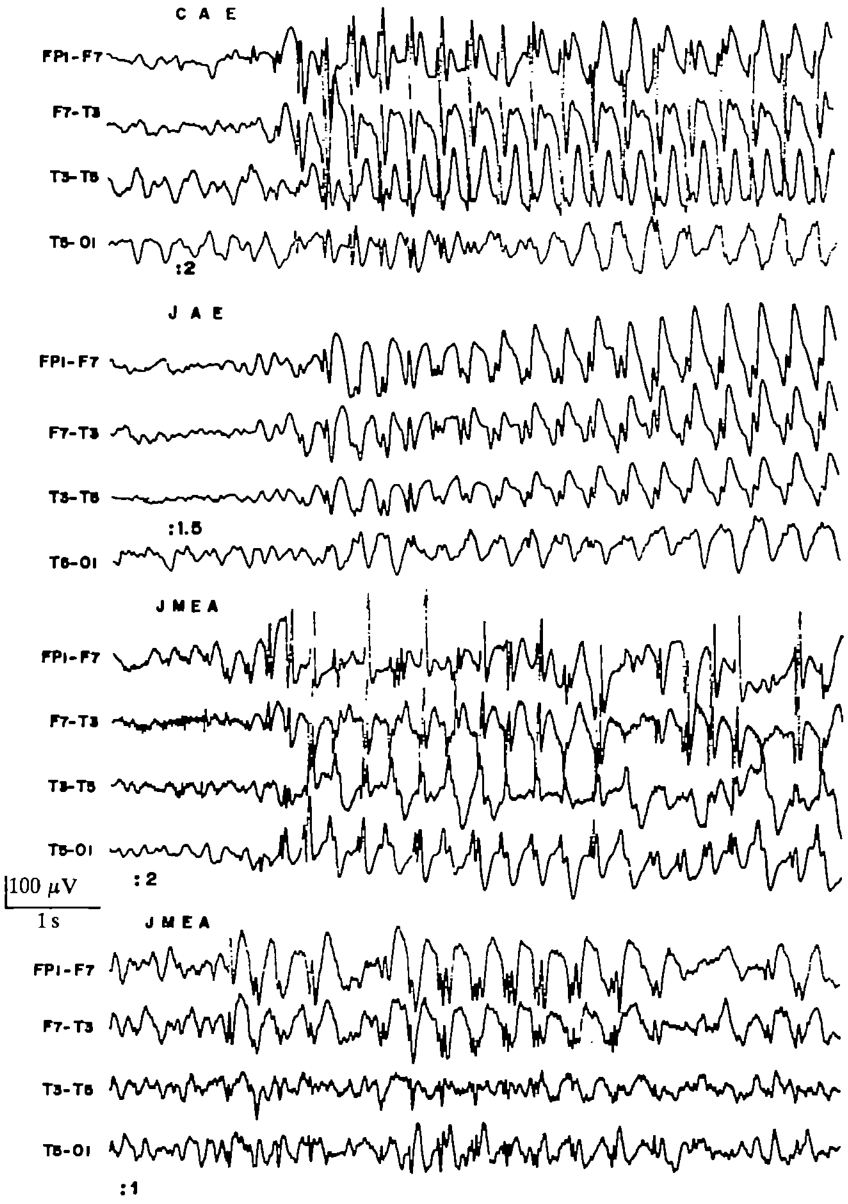


FIG. 7. Onset and characteristics of video-EEG discharges in CAE, JAE and JMEA. The differences described in the text are apparent.

Significant qualitative differences were found mainly in JMEA (figs 4, 5, 7). The discharges in JMEA consist of single/double/triple or multiple spikes, usually preceding or sometimes superimposed on the slow waves. The multiple spikes may be as many as 8 with a characteristic 'worm-like' appearance or compressed Ws. The number and amplitude of spikes show considerable inter- and intradischarge variation. The slow waves of the complexes may 'miss' their spikes or, conversely, the spikes/multiple spikes may be much higher than their corresponding slow wave or even appear in the course of another complex (figs 4, 5, 7). The frequency of the discharges is usually from 2.5–4.5 Hz but complexes as slow as 2 Hz or as rapid as 7 Hz were seen frequently. This irregularity of frequencies amongst neighbouring spike-wave complexes in JMEA is very characteristic (figs 4, 7). The onset usually, but not invariably, consists of fast 3.5–4.5 Hz followed by complexes of variable, commonly 2.5–3.5 Hz spike-slow waves. There is no smooth, regular, slowdown of the frequency of the discharges after the initial phase. The frequency at the end of the discharge may be higher, equal to or slower than that of the initial phase (Table 4). Another important observation is that the discharges were frequently fragmented (figs 4, 7). Discharge fragmentation consists of transient discontinuations of a regular and rhythmical discharge, either by slow waves and/or complexes of different frequencies or by a true pause followed by a rapid (within 1 s) reactivation of the paroxysm (figs 4, 7). Pauses of longer duration were also seen frequently (clusters or series of discharges).

Discharge fragmentations and compressed Ws observed in JMEA patients with spike-wave discharges vary quantitatively from patient to patient and from discharge to discharge. Discharge fragmentations were more pronounced in older patients while Ws were more abundant in the younger group of childhood JMEA. Conversely, none of the children with CAE showed discharge fragmentations or Ws. The discharges were rhythmic with gradual slowing from onset to termination (fig. 1). There was no intradischarge frequency variation of the complexes. The spikes were usually single or double, never more than 3 per spike-wave complex, with no abrupt variations in amplitude and relationship to the slow waves. No discharge fragmentations were observed. In JAE, the discharges have an intermediate position between CAE and JMEA (figs 2, 3, 7). Discharge fragmentations were observed in 3 discharges, multiple spikes resembling Ws consistently seen in the discharges of 1 patient (fig. 3) and the relation of spikes-slow waves was not always fixed. However, the discharges in JAE were rhythmic, with regular slowing from onset to termination, no abrupt variations in amplitude and number of spikes (figs 2, 3), thus having more similarities with CAE than JMEA.

In MAE, the discharges were rhythmic with an opening ictal phase from 4–5 Hz with smooth and regular slowing to 3.1 Hz at termination (fig. 6, Table 4). The spikes of the complexes varied in numbers from 1–6 but did not show the sudden amplitude variations seen in JMEA. Furthermore, no discharge fragmentations were observed.

DISCUSSION

The classification of the 20 patients into the epileptic syndromes was based on firm clinical and EEG criteria as laid down by the ILAE (Commission of the ILAE, 1985). This study shows that typical absence seizures in the epileptic syndromes have different clinical and EEG manifestations which have not been reported previously. In MAE, the manifest rhythmic myoclonic jerks make the diagnosis unmistakable and will not be discussed further.

Consciousness is severely impaired in CAE. However, the patient retains reflex responses to visual threat, pain and sometimes auditory stimuli. Recollection of ictal events is abolished with a few exceptions in which the patient may remember verbal or other orders administered towards the end of the seizure. A similar, but less severe situation is observed in JAE. The main difference is that some awareness and recollection of ictal events may be preserved in the latter. Conversely, in JMEA, consciousness is much less impaired and requires specific tests for clinical detection. The degree of impairment of consciousness in JMEA appears to be age-related.

Expressive speech is abolished in CAE. It may be retained for up to 2 s after the onset of the EEG paroxysms but there was no occasion when speech or verbal responses were obtained in the remainder of the attack. A few words uttered at the onset of the discharge were comprehensible, not dysphasic, with occasional dysarthric elements. A similar, but less severe situation is observed in JAE. Expressive speech is abolished but patients may continue their preictal verbal activity in some of their seizures, stop and resume during the attack. When the patients resumed speaking, the words were usually out of sequence but they were always related to the topic with which they were concerned previously, that is, they could say a number if they were counting or a word or phrase if they were reciting. Their speech was sometimes dysarthric but never dysphasic. In JMEA, speech is intact although a situation similar to CAE and JAE is not uncommon in children. On a few occasions, the adolescent patient with JMEA may be dysarthric, stutter or briefly discontinue his speech.

Comprehension of speech is abolished in CAE with a few exceptions towards the end of the attack where it may be retained as evidenced by postictal recollection. It is also disturbed in JAE but not as severely as in CAE. Thus patients with JAE may recollect phrases given to them at any time during the attack in some seizures and even respond correctly to verbal orders or questions administered during the discharge. In JMEA, comprehension of speech is usually intact although a situation similar to that in JAE may be observed in children.

In typical absences, expressive speech is more severely affected than receptive speech, irrespective of the epileptic syndrome. Thus some patients were able to respond to verbal orders correctly and remember sentences or words given to them during the attack while they were unable to speak or repeat words which they may have remembered after the cessation of the seizure. However, spontaneous expressive speech may also be retained as shown in the absence seizures of JAE and JMEA.

Cessation of OB within a mean of 1.4 s was observed in CAE seizures. Similarly, OB usually stops in JAE, but often long after the onset of the discharge. On other occasions, it may slow in depth and rate or may continue for the whole duration of the attack. In adolescent patients with JMEA, OB is not usually interrupted.

The eyes opened within 2 s of the onset of the ictal discharges in CAE only. There was not a single absence seizure in CAE in which the eyes remained closed after 2.5 s from the onset of the EEG paroxysms. Conversely, the eyes usually were closed at seizure onset in JAE and JMEA or infrequently opened 3 s after the onset. Therefore, opening of the eyes within 2.5 s of the onset of the discharge, a consistent and easily discernible clinical sign, could be used as a criterion to differentiate CAE from other JAE and JMEA absences.

Another traditional teaching is that the eyes rotate upwards, stare and remain still during typical absences (Janz, 1969; Penry *et al.*, 1975; Commission of ILAE, 1985). This was not the case in nearly all our patients with JAE and JMEA. Even in CAE, the eyes frequently move 'spontaneously' or towards external stimuli and the so-called 'blank' expression is often not discernible when seizures are reviewed in mute-video fashion without their EEG accompaniments.

Automatisms were observed in all patients with CAE and JAE in at least one of their seizures. They varied greatly in complexity, location and character from seizure to seizure, the same patient having simple and complex absences. Simple absences occurred more often in patients with JAE, particularly when they were not exposed to external stimuli and were not involved in demanding preictal activities such as reciting and holding objects. Automatisms were rare in JMEA but they did occur in some patients with clinically detectable impairment of consciousness.

Automatisms in absence seizures have been studied extensively (Penry and Dreifuss, 1969; Penry *et al.*, 1975; Stefan *et al.*, 1982; Holmes *et al.*, 1987). This study confirms that automatisms, de novo, perseverative or both, are common and mainly orofacial. However, certain other aspects are new. A significant finding is that automatisms can be evoked and their pattern and distribution can be changed by passive movements, postural repositioning or other ictal stimulation of the patient. This confirms the notion that automatism is automatic behaviour released by clouding of consciousness (Gastaut *et al.*, 1973). Furthermore, the significance of the classification of absence seizures as simple and complex as well as their various subdivisions (Penry and Dreifuss, 1969; Gastaut *et al.*, 1973; Commission of ILAE, 1981) is undermined, as they can serve descriptive purposes only. The same applies to the cephalocaudal distribution of the automatisms and their significance as reported by Stefan *et al.* (1982). This study showed that a simple absence seizure can be transformed to a complex one through ictal activation of a group of muscles by appropriate passive movements which often result in automatisms performed by the same and related muscles. Similarly, an automatism can be initiated in a hand and precede orofacial ones which may not even occur. From the clinical point of view, automatisms are not stereotyped in absence seizures and this may serve in the differential diagnosis from complex partial seizures on the few occasions where difficulties may arise.

Previous reports on the EEG of absence seizures in CAE, JAE and JMEA have concentrated mainly on the frequency and the duration of the discharges (Commission of ILAE, 1981, 1985). This study confirms that the seizures are significantly longer in JAE and shorter in JMEA while CAE has an intermediate position. However, quantitative analysis of the frequencies in various sections of the discharges showed that no significant differences exist in their opening phases. The reported higher frequency of the ictal paroxysms in JMEA (Janz, 1969; Delgado-Escueta and Enrile-Bacsal, 1984; Wolf, 1985) may be attributed to fast spike-slow wave complexes, sometimes as rapid as 6 Hz, which are seen frequently in the opening phase of the paroxysms. However, they are usually interposed with slow complexes, sometimes at 1-2 Hz. Another interesting finding in this study is that slowing of the discharge occurs mainly within the first few seconds of the opening phase of the attack, irrespective of syndromic differences.

Qualitative differences appear to be more striking than the above quantitative ones. Thus EEG absence paroxysms with Ws and discharge fragmentations are highly characteristic of JMEA.

In conclusion, absence seizures in epileptic syndromes show significant clinical and EEG differences which should be appreciated in their classification and study. Certain traditional aspects of typical absences have been challenged by our observations.

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TROPICAL SPASTIC PARAPARESIS AND HUMAN T CELL LYMPHOTROPIC VIRUS TYPE 1 IN THE UNITED KINGDOM

by J. K. CRUICKSHANK,[1] P. RUDGE,[1,2] A. G. DALGLEISH,[1]
M. NEWTON,[2] B. N. McLEAN,[2] R. O. BARNARD,[2] B. E. KENDALL,[2]
and D. H. MILLER[2]

(*From* [1]*Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex, and* [2]*The National Hospitals for Nervous Diseases, Queen Square and Maida Vale, London, UK*)

SUMMARY

Twenty-one patients with tropical spastic paraparesis (TSP), all of whom were born in the Caribbean and who had migrated to the United Kingdom, are described. All had a progressive spastic paraparesis developing many years after immigration and all 19 tested had antibodies to the human T cell lymphotropic retrovirus type 1 (HTLV1). The clinical and laboratory features and visual, auditory and somatosensory evoked potentials are described. Details of magnetic resonance scanning of the brain and, in a few cases, the spinal cord are compared with those found in multiple sclerosis. The antibody titres to HTLV1 assessed by particle agglutination, Western blot, antibody-directed cell mediated cytotoxicity and pseudotype neutralization were higher than in asymptomatic infected relatives and in patients with adult T cell leukaemia. Some, but not all, of the IgG oligoclonal bands in the CSF were directed against HTLV1. IgM oligoclonal bands directed against HTLV1 were found in 2 patients. Sixty of the 64 first degree relatives of 11 Jamaican patients with TSP were traced in the UK and the Caribbean; 20–30% of those born in the Caribbean had antibodies to HTLV1, irrespective of their present place of residence, whilst none of those born in the UK, who were the children of the patients, had antibodies. The original pathological material obtained from the Caribbean by Montgomery *et al.* (1964) is reviewed. These results are discussed in relation to animal retroviral neurological diseases, particularly visna in sheep which has clinical and pathological features closely similar to TSP. It is proposed that TSP is due to a HTLV1 infected lymphocyte/macrophage immune-mediated inflammatory response in the spinal cord.

INTRODUCTION

Progressive paraparesis of unknown cause is a common neurological problem both in temperate and tropical regions. A substantial proportion of white patients of European origin living in temperate zones, in whom extensive clinical investigation was unrevealing, prove at autopsy to have demyelination of the type seen in multiple sclerosis (MS) (Marshall, 1955), a conclusion supported by magnetic resonance imaging (Miller *et al.*, 1987). In contrast to this, spastic paraparesis in the tropics is

Correspondence to: Dr P. Rudge, National Hospital for Nervous Diseases, Queen Square, London, WC1N 3BG, UK.

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rarely due to MS. There are obvious difficulties in excluding other diagnoses in countries where investigation facilities such as detailed myelography and nuclear magnetic resonance scanning are not readily available and disorders such as lathyrism, nutritional deficiencies and infections account for the paraparesis in some patients. However, it is clear from the work of E. K. Cruickshank and his colleagues in the West Indies, described in detail by Montgomery *et al.* (1964), that there is a group of native patients who have a relatively uniform clinical picture of progressive paraparesis in whom known causes have been excluded. In a series of papers these workers drew attention to the high frequency of the disorder, which they called Jamaican myelopathy, in the West Indies (Cruickshank, 1956; Cruickshank *et al.*, 1961; Rodgers and Cruickshank, 1962; Montgomery *et al.*, 1964; Cruickshank, 1973). They pointed out that positive serology for syphilis or yaws was found in some, but not all cases and that there was no difference in the clinical picture in those with positive and those with negative serology. Postmortem material was obtained from a number of patients but no clear aetiological factors emerged (Montgomery *et al.*, 1964; Robertson and Cruickshank, 1972).

A major advance in understanding this condition occurred when Gessain *et al.* (1985) demonstrated that the human T cell lymphotropic type 1 retrovirus (HTLV1) was associated with spastic paraparesis in the West Indian island of Martinique (Vernant *et al.*, 1987). The condition is now commonly known as tropical spastic paraparesis (TSP) and the association with HTLV1 has been confirmed throughout the Caribbean (Rodgers-Johnson *et al.*, 1985; Morgan *et al.*, 1988) and extended to migrants from that region (Newton *et al.*, 1987). A similar neurological condition has been described in other areas where HTLV1 infection is endemic, most notably in South Japan, where it is called HTLV1-associated myelopathy (HAM) (Osame *et al.*, 1987), the Seychelles (Roman *et al.*, 1987) and Columbia (Zaninovic *et al.*, 1988).

The purpose of the present paper is to review the clinical features of progressive paraparesis of unknown cause (hereafter termed TSP) in West Indian migrants to the UK, to assess the HTLV1 antibody status of both the patients and their relatives, systematically to determine the laboratory features including visual, auditory and somatosensory evoked potentials, cerebrospinal fluid (CSF) abnormalities and nuclear magnetic resonance image (MRI) appearances of TSP, and to review the pathology of the original material from the 1964 Jamaican series deposited at the neuropathology department at Maida Vale Hospital, London. Finally, we compare the clinical and pathological features of TSP and neurological disorders of animals known to be due to retroviruses.

METHODS

Patients

Patients with a provisional diagnosis of TSP were sought from medical records indices at the National Hospitals, Queen Square and Maida Vale, London, by looking for TSP, Jamaican neuropathy, Jamaican myelopathy and MS in people of West Indian origin. In addition, other neurologists in the London area were asked if they had seen any such patients in the previous 10 years. A diagnosis of TSP was accepted if, after clinical review and examination by 1 of 3 authors (K.C., M.N., P.R.), the patient had evidence of a paraparesis for which there was no alternative explanation after full investigation (at least one normal full myelogram was obligatory) and the patient was born in the Caribbean. The first 21 patients with TSP form the basis of this report. Three patients, all born in the West Indies, with clinically definite MS (Poser *et al.*, 1983) were also reviewed and had MRI scans and HTLV1 antibody studied. Patients with MS who were born in the UK but had Caribbean ancestors were not included in this study. The laboratory assessing the HTLV1 status did not know the diagnosis before testing specimens.

First degree relatives, including spouses and cohabiting partners, of 11 Jamaican-born TSP patients were traced and blood obtained from 60 of 64 of those living in Jamaica or UK; 5 relatives who were alive at the time of the study but resident in the USA were not contacted. There were no other known relatives.

Neurophysiological studies

Visual (VEP), auditory (AEP) and somatosensory (SEP) evoked potentials were obtained using standard methods (Halliday, 1982). Electromyography and sensory and motor conduction velocities of the fastest fibres were obtained using routine techniques.

Magnetic resonance imaging

All patients were examined on a Picker 0.5 Tesla superconducting NMR imager. In all, axial sections of the brain were made using a spin-echo multislice sequence (SE 2000/60) with 5 mm contiguous slices. The cervical segment of the spinal cord was imaged in 6 patients using a saddle-shaped surface coil; in 3 cases the dorsal cord was also examined using a planar coil. Contiguous 5 mm multislice images were made using a SE 500/40 sequence clearly to depict the anatomy and SE 1500/80 to detect any pathology with increased T2 relaxation time.

HTLV1 antibodies

The immune response against HTLV1 in patients with TSP, their relatives and patients with adult T cell leukaemia (ATL) was examined by immunofluorescence on HTLV1 producing C19/PL cells (Tedder *et al.*, 1984), Western blot (Thorpe *et al.*, 1987), enzyme linked immunoabsorbent assay (ELISA, Dupont kit) (Saxinger and Gallo, 1983), particle agglutination (Serodia kit) (Ikeda *et al.*, 1984), antibody-directed cell mediated cytotoxicity (Miyakoshi *et al.*, 1984) and pseudotype neutralization (Clapham *et al.*, 1984). Immunofluorescence, ELISA and particle agglutination assays are sensitive tests for the presence of antibodies to the virus, the antibody-directed cell mediated cytotoxicity and pseudotype neutralization assays detect functional antibodies directed at different epitopes on the envelope protein. The Western blot technique was used to examine whether antigens recognized by the antibodies from patients with TSP are the same as those from asymptomatic and ATL patients.

Cerebrospinal fluid

Oligoclonal IgG banding. CSF samples were analysed in parallel with serum where possible. Isoelectric focusing (IEF) of IgG was performed after the method of Moyle *et al.* (1984). Samples were stored at 4° C, or frozen at 035° C. These latter samples were thawed once only, immediately before testing. The total protein was estimated by turbidimetry using benzethonium chloride and identical amounts of protein (2 μg) were focused by diluting serum in water (approximately 1/400) and running the CSF neat. Samples were loaded using an application foil onto 1 mm thick agarose IEF gels with pH gradient of 3-10.5 made in the laboratory (Seakam agarose 0.3 G; Pharmacia ampholytes 2-10, 2 ml; 8-10.5, 0.5 ml; 10% glycerol, 27 ml; D-sorbitol, 3.6 G). The samples were focused using an LKB IEF tank at 20 W, 1 500 V, 150 mA for 1 500 V/h, and then protein was passively transferred to a nitrocellulose membrane by pressure for 20 min. The membrane was blocked with 1% albumin for

30 min, followed by 45 min incubation with 1/1 000 goat antihuman Fc specific IgG and then washed four times with 0.05 M phosphate-buffered saline pH 7.2/0.1% Tween 20/0.1% albumin (PBST) and twice with distilled water. Incubation with 1/1 000 rabbit antigoat IgG-HRP conjugate for 45 min was followed by further washing with PBST and water before visualization with 4-amino 9-ethylcarbazole. In 7 patients IgM was sought by substituting appropriate IgG antibodies with IgM.

HTLV1 antigen blotting

Anti-HTLV1 IgG. The method of Dörries and Ter Meulen (1984) was used. In brief, the nitrocellulose membrane was incubated overnight at 4° C with purified HTLV1 virus derived from cell line C91/PL at a loading dose of 10 $\mu g/cm^2$. Unoccupied sites on the membrane were blocked with 1% albumin/1% gelatin for 30 min. IEF of samples was run as described above and antibody passively transferred to the antigen-coated membrane by pressure for 20 min. The membrane was washed, incubated with antibodies and stained to visualize distinct bands produced by IEF.

Anti-HTLV1 IgM. The same method as above was used except goat antihuman IgM Fc specific antibody was used as the first antibody.

RESULTS

Clinical features

The population (Table 1)

There were only 2 men in this series of 21 patients. The age at the time of the study ranged from 43–73 (mean 56) yrs and age at onset of the symptoms ranged from 20–68 (mean 46) yrs. Disease duration was 1–23 (mean 10) yrs. By definition, all

TABLE 1. DEMOGRAPHIC DATA

Case no.	*Sex*	*Age (yrs)*	*Island of birth*	*Time in UK (yrs)*	*Age at onset (yrs)*	*Duration of disease (yrs)*
1	F	61	Trinidad	30	59	1
2	F	55	Jamaica	30	51	4
3	M	53	Jamaica	29	49	4
4	F	53	Montserrat	26	51	2
5	F	48	Jamaica	26	47	4
6	F	65	Jamaica	35	52	13
7	F	53	Jamaica	26	47	6
8	F	49	Jamaica	29	37	12
9	F	48	Jamaica	26	39	9
10	F	52	Jamaica	32	36	16
11	F	53	Jamaica	25	42	9
12	F	61	Jamaica	23	54	7
13	F	54	St Kitts	?	44	10
14	F	49	St Kitts	26	38	11
15	F	48	Jamaica	26	33	15
16	F	60	Montserrat	30	40	20
17	F	59	St Vincent	27	40	19
18	M	43	Trinidad	30	20	23
19	F	63	Jamaica	24	53	10
20	F	73	Jamaica	33	63	10
21	F	69	Trinidad	42	68	1
Mean		56		29	46	10

patients came from the Caribbean, their places of birth being Jamaica (13), Montserrat (2), Trinidad (3), St Kitts (2) and St Vincent (1). All patients were resident in London, UK, and had immigrated 23-42 (mean 29) yrs before. Some had made short trips of less than 6 wks duration back to the Caribbean for holidays.

Symptoms

Initial symptoms. Sensory symptoms in the lower limbs, often accompanied by bladder disturbance or limb weakness, were the predominant features in the first few weeks or months of the illness in the majority (17/21) of the patients. Pain in the lower limbs, often radiating from the buttocks to the feet, occurred in 15/21 patients. This pain was accompanied by static back pain in the lumbar region in some cases (8/21) and back pain occurred in isolation in 3 patients. The sciatic pain was variously described as aching, tingling, burning or sharp in character. It was sometimes made worse by activity. Other sensory symptoms were unusual as the initial complaint, but numbness and supersensitivity of the soles of the feet each occurred in 1 patient at the onset of their illness.

The bladder symptoms, which were the sole initial complaint in 1 patient, comprised nocturia, urgency and frequency of micturition (12/21); 1 patient had incontinence of urine at the onset.

Leg weakness was an unusual initial complaint in isolation (3/21) but was associated with sensory and bladder symptoms in half the patients. It was often described as heaviness or stiffness rather than loss of power although 1 patient said she suddenly developed weakness of one leg. The motor symptom was unilateral at onset in 5/21 patients but in the majority was bilateral.

No patient had upper limb symptoms as the initial complaint.

Apart from 3 women stating that their initial symptoms occurred within 3 months of childbirth there were no obvious factors related to the onset of the disorder.

Progression. The course of the disease was determined from the history as no patient was seen throughout by one observer, thus allowing only an approximate idea of progression.

Motor symptoms, confined to the legs in spite of occasional signs in the arms, replaced sensory problems, usually within a few months of onset of the disease. The most frequent pattern was a progressive deterioration of gait over 2–10 yrs to a plateau of moderate or severe disability (disability status scale scores of 6–8; Kurtzke, 1965); 5 patients were wheelchair bound within 7 yrs (1 within 1 yr) and all but 2 of the others, both with short disease duration of 2 and 4 yrs, respectively, needed assistance for walking by 7 yrs. Occasionally progression of the gait disturbance ceased for 2–4 yrs (3/21) before further deterioration occurred; in 2 patients, who are still ambulant, the disability seems to have levelled out. Three patients have improved after receiving cortico-steroids; 2 were given high doses of methyl prednisolone intravenously (2.5 g over 5 days) in an attempt to modify the disease while a third patient was treated with low dose prednisone and methotrexate for concomitant arthritis.

The sensory symptoms in the legs lessened with time but the back pain persisted in 10/21. Minor paraesthesiae, numbness and burning discomfort in the lower limbs, especially the feet, were frequently admitted on direct questioning. Bladder disturbance became an increasing problem, incontinence developing in 5/21. Constipation developed in all patients and impotence occurred in the 2 male patients.

Current clinical status

By definition, all patients had a spastic paraparesis although in 1 the spasticity disappeared in the late stages. The paraparesis was severe in 90%; 7 patients were confined to a wheelchair permanently, 3 used a wheelchair intermittently, 9 needed walking aids and 2 could walk with difficulty unaided. The paraparesis was moderate to severe in those who could walk, while those confined to a wheelchair were virtually plegic. The paraparesis was symmetric in 14/21, asymmetric in 6/21 and was essentially unilateral in 1 patient. The knee jerks were brisk and the plantar responses extensor in all patients; in 3 patients the ankle jerks were absent. Focal neurogenic wasting was not obvious in any patient, although the muscles were often thin in the plegic subjects. Any ataxia was slight and commensurate with the degree of weakness.

Weakness of the distal parts of one or both upper limbs occurred in 3/21 patients. One of the patients had fasciculation, without wasting, of the upper limb musculature and diminished reflexes. The other two had pathologically brisk tendon reflexes in the upper limbs as did the majority of the remaining patients.

Sensory signs were not marked and were confined to the lower limbs. In 7 patients there was minor impairment of pin prick appreciation in the lower legs and feet and 6 had slight impairment of light touch appreciation over the feet. One of these patients had a partial Brown-Sequard syndrome and 1 additional patient had a vague sensory level at the sixth thoracic dermatome. Vibration sensation was diminished or absent at the ankles in 6 patients and sense of passive movement was slightly impaired in 2.

Urinary incontinence was present in 5/21 patients and 18/21 had frequency and urgency of micturition. The bowel disturbance persisted in all patients, as did the impotence in the 2 men. The cranial nerves were normal in all with the exception of 1 patient with unilateral hearing loss due to barotrauma. Visual acuity was 6/9 or better in all patients; colour vision was assessed in 11 patients and was normal in all except 1 who was mildly impaired in one eye; no patient had field defects on clinical testing; the optic discs were normal in all.

Associated diseases

A variety of other disorders was found in our TSP patients including single examples of cancer of the breast, inflammatory arthropathy of unknown type, renal calculi, and diabetes. Two patients had mitral valve disease, including 1 who developed an undiagnosed granulomatous disease from which she died. One patient had a cervical laminectomy for mild cord compression without any beneficial effect on the course of the paraparesis. Three other patients had evidence of mild cord compression on MRI many years after the onset of their symptoms; all had normal myelograms earlier in the course of their illness.

VDRL/TPHA/FTA was positive in the serum in 8/21 patients and negative in the CSF in all. Anticardiolipin (phospholipid) antibodies were negative in 14, and borderline positive in 2, of the 16 patients tested.

Neurophysiological testing (*Table 2*)

Visual evoked potentials. VEPs were abnormal in 10 of the 19 patients tested, principally with delayed latency of the P100 component; occasionally low amplitude or degraded waveforms were seen. The delay ranged from only a few milliseconds outside the normal range for age and sex to marked prolongation. In 2 patients the abnormality was unilateral but in the remainder was bilateral. In the latter, the latency abnormalities were identical in 4 from either eye and the interocular latency difference was 12 ms or less in the other 4. The P100 latency can increase with time despite preservation of visual acuity (fig. 1).

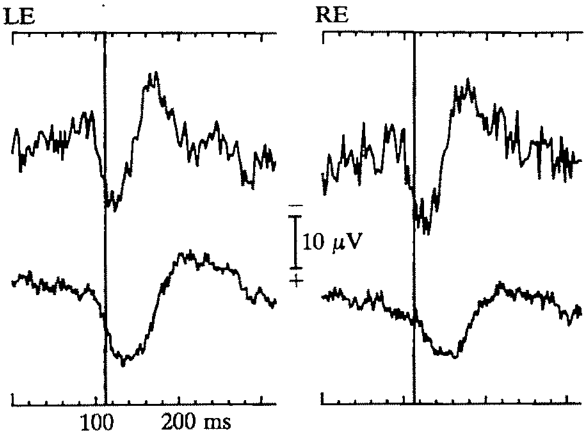

FIG. 1. VEP from left eye (LE) and right eye (RE) from *Case 15* at age 38 yrs (*above*) and 49 yrs (*below*). VA 6/5 in both eyes. Note increase in latency of abnormal P100 between first and second record. Record obtained from midline channel 5 cm above inion referred to Fz.

Auditory evoked potentials. AEPs were recorded in 16 cases; 4 were unequivocally abnormal including that from the patient with traumatic hearing loss. The abnormalities were usually mild with slight prolongation of latencies of brainstem components or, occasionally, loss of some of these components. Two other patients failed to show any brainstem potentials but in these patients muscle artefact rendered interpretation difficult.

Somatosensory evoked potentials. SEPs from the upper limbs were abnormal in 11 of 17 patients studied. Only 1 patient showed an unequivocally delayed peripheral

TABLE 2. VISUAL, AUDITORY AND SOMATOSENSORY EVOKED POTENTIAL LATENCIES (ms) IN TSP

			AEP										*SEP*							
	VEP		*I*		*II*		*III*		*IV*		*V*		*N9*		*N13*		*N20*		*P40*	
Case no.	*L***	*R***	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*
2	103	102	1.5	1.6	3.1	3.0	4.1	3.9	5.4	5.6	6.0	5.9	10.6	10.8	14.6	15.2	20.3	20.1	0	0
4	107	105	1.5	1.6	2.4	2.6	3.4	3.6	—	—	5.3	5.2	9.8	10.0	16.2*	16.1*	21.0	21.0	0	0
5	107	107	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	134*	135*	+	+	+	+	+	+	+	+	+	+	+	+	—	—	22.5	24.0*	—	—
7	111	111	1.5	1.5	2.9	3.1	4.2	4.2	5.3	5.4	6.0	6.0	10.2	10.2	14.3	15.8*	20.4	20.4	0	0
8	116*	123*	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	106	103	1.6	1.6	2.8	2.9	3.8	3.8	—	—	5.5	5.4	10.0	9.7	—	—	24.2*	23.4*	0	0
10	110	110	1.7	1.6	3.2	3.3	4.5	4.7	5.8	5.7	6.7*	6.8*	11.4	11.4	15.5	15.5	21.8	22.0	49.5	51.5
11	109	107	1.3	1.4	3.0	2.8	4.0	3.9	5.3	5.0	5.9	5.9	9.2	9.3	13.8	13.3	20.0	19.1	39.0	40.2
12	142*	135*	1.7	1.7	2.8	—	3.9	3.9	5.4	5.6	6.1	6.4	10.0	10.0	12.7	12.9	23.9*	24.0*	57.0*	55.8*
13	125*	128*	1.9	1.8	3.3	3.4	4.2	4.3	5.4	5.4	6.1	6.5*	13.6*	12.6*	15.6*	16.2*	24.5*	24.3*	—	—
14	117*	116*	+	+	+	+	+	+	+	+	+	+	11.3	+	15.9*	—	25.7*	22.9*	+	52.3
15	139*	151*	1.8	1.8	2.8	—	3.6	—	6.2	—	7.9*	—	10.3	10.3	—	—	26.3*	26.3*	—	—
16	109	117*	1.9	—	2.9	—	4.2	—	5.2	—	5.8	—	10.1	10.1	+	13.3	19.5	19.5	0	0
17	118*	117*	2.0	2.0	2.8	3.1*	3.5	4.3*	4.6	5.4	5.9	5.8	10.0	12.0	14.3	13.9	20.4	20.4	—	64.8*
18	101	100	1.7	1.6	2.9	3.0	4.1	4.1	5.5	5.3	6.0	5.8	11.5	11.8	16.0*	16.5*	20.8	21.9	55.5*	48.5*
19	0	0	0	0	0	0	0	0	0	0	0	0	9.9	9.9	14.4	14.1	20.2	19.8	0	0
20	129*	140*	1.7	1.6	3.0	2.5	4.4*	4.0	—	—	6.2	6.1	10.2	11.6	16.7*	—	21.8	22.2	0	0
21	120*	111	1.8	1.5	2.5	—	4.0	—	5.4	5.2	6.1	6.0	9.4	9.4	—	—	23.1*	22.8*	0	0

** L = left, R = right; — = absent component; + = unreliable record; 0 = record not obtained; * = latency 2.5 SD from mean of normal age/sex matched population.

N9 component but in 3 others this component could not be consistently recorded from one (2) or both sides. Increased latency or loss of the N13 spinal component was a feature of all but one of the abnormal upper limb SEPs obtained (fig. 2) whereas delay of the cortical N20 component was seen in 7 (fig. 3). Besides delay of the N13 component, attenuation of that waveform was also evident and occasionally broadening and separation of the N13 wave could be seen. Lower limb SEPs were performed in 9 patients, 3 of whom had no cortical responses and 3 showed delayed P40 components (fig. 4). Three patients had normal P40 latencies. Of 5 patients with mild sensory signs, 4 had abnormal SEPs from the lower limbs.

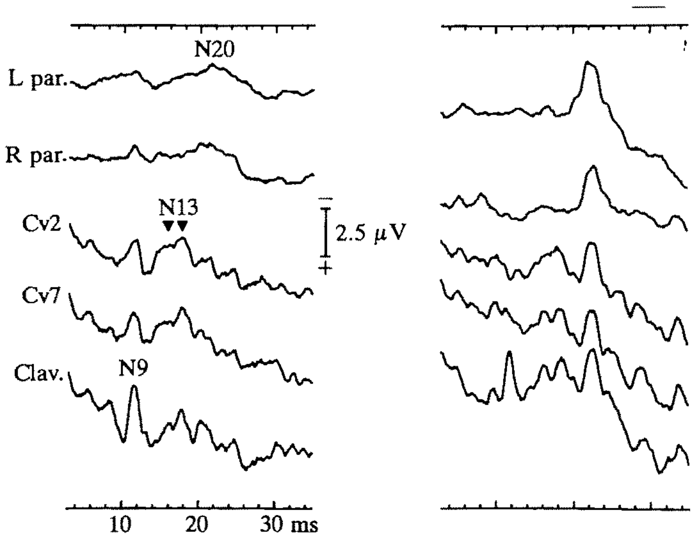

FIG. 2. SEP from left (*at left*) and right median nerve stimulation in *Case 18*. Note degraded and delayed component N13 with normal component N20. Electrodes placed at left and right parietal region, cervical vertebrae 2 and 7, and clavicle (from above down) and referred to Fz.

Electromyography (EMG) and peripheral nerve conduction studies. Sensory (sural and median nerves) and motor (median, ulnar and common peroneal nerves) conduction velocities were normal in all 10 patients tested. Recordings of H reflexes and F waves were not made. Only 2 patients had evidence of chronic partial denervation in the lower limbs (tibialis anterior, quadriceps) and 1 of these had abnormalities in the upper limbs. Maximum discharge rates of the motor units in the lower limbs were low in all patients studied.

Cerebrospinal fluid

Cells. Results of CSF examination obtained at lumbar puncture were available for 19 of the 21 patients. Some patients had more than one lumbar puncture. Ten of the patients showed a pleocytosis of 5 or more cells/mm^3, two of whom had a count of 20 and 55 cells/mm^3, respectively. There was no obvious trend in the cell count in

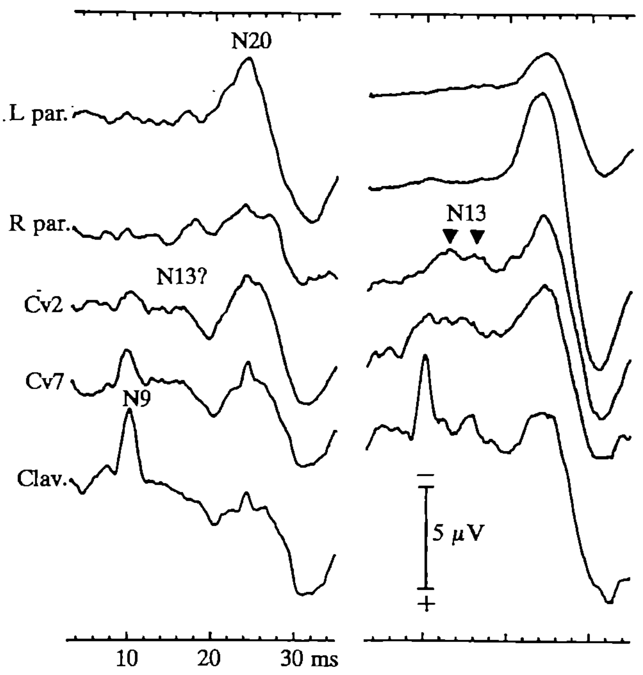

FIG. 3. SEP from left (*at left*) and right median nerve stimulation in *Case 12*. Note increase in latency of N20 on stimulation of either side and degraded components N13. Montages as in fig. 2.

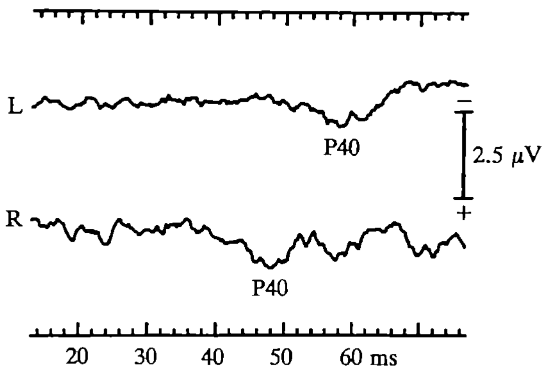

FIG. 4. SEP from tibial nerve stimulation (L = left, R = right) in *Case 18*. Electrodes placed 2 cm posterior to vertex and referred to Fz. Note asymmetric latency increase from either side.

those patients who had repeated lumbar punctures or when the cell count was plotted against duration of symptoms for the whole group. The cells were usually reported as lymphocytes; most data were collected before the characteristic multilobulated nucleus of lymphocytes with HTLV1 infection was described (*see* below).

Protein. The protein content in the CSF was greater than 0.4 g/l at some time during the course of their illness in 7 patients. In 6 of these the level was always less than 0.8 g/l; the exception was a patient from whom 3 CSF samples were obtained over a period of years and in which the protein levels were 0.5, 1.4 and 0.6 g/l, respectively. No patient had a positive fluorescent treponemal antibody test in the CSF.

Oligoclonal IgG bands. There were 13 patients in whom IEF of the IgG could be analysed; all had oligoclonal bands. In 2 of these patients no serum analysis was run in parallel so that evidence of local synthesis within the CSF could not be established; 1 patient had an identical serum and CSF pattern, indicating leakage of the bands from the former. The remaining 10 patients all had evidence of local synthesis of oligoclonal IgG and in 8 of these some, but not all, bands were common to the CSF and serum. Three of these patients also had a clear monoclonal band in both serum and CSF.

Antigen blotting. Nine CSF samples (from 7 patients) were examined; all had an oligoclonal IgG pattern and 2 had an additional monoclonal band (*see* above). After immunoblotting against HTLV1, 5 patients had an oligoclonal pattern in the CSF alone. The other 2 patients showed only a diffuse polyclonal uptake no greater than that seen in the serum although more than that in control subjects or patients without neurological disease. The monoclonal patterns seen in 2 patients in the total IgG IEF did not blot against HTLV1 in either case.

The 2 patients with no apparent IgG activity against HTLV1 were subsequently found to have specific anti-HTLV1 IgM in the CSF.

Haematology and immunological studies

In all 16 patients in whom peripheral blood films were studied, lymphocytes with convoluted nuclei were found, comprising 2–5% of the total lymphocyte count; some of these cells resembled immunoblasts. We have previously reported that cultures of these cells reacted with monoclonal antibodies anti-P19 and HT462 in a pattern similar to that observed in cultured cells infected with HTLV1 and that lymphocytes from 50% of the patients express IL2 (Dalgleish *et al.*, 1988).

Of the 21 patients, serum was obtained from 19 for HTLV1 assays. All were positive by immunofluorescence, IgG ELISA and polyclonal particle agglutination tests. Western blots of the TSP sera were of stronger intensity than most of the sera from asymptomatic relatives or from patients with ATL. One TSP sera titred out at 1:32000 (fig. 5). The antibodies were primarily directed against the core proteins P24, P18, the precursor P53 and the envelope glycoprotein GP62. The antibody titres against HTLV1 on the particle agglutination test were significantly higher in the TSP sera (geometric mean 1:46000) than in sera from infected relatives (1:2700, $P = 0.014$) or patients with ATL (1:3200, $P < 0.01$). The titres were also higher in the TSP sera on the ELISA assay (1:1500–1:15000) than in the other groups; however, 1 relative had a titre of 1:30000, higher than any patient. Similarly the antibody-directed cell mediated cytotoxicity and pseudotype neutralization titres were higher in the TSP patients than in the other infected subjects but the differences only reached significance between TSP patients

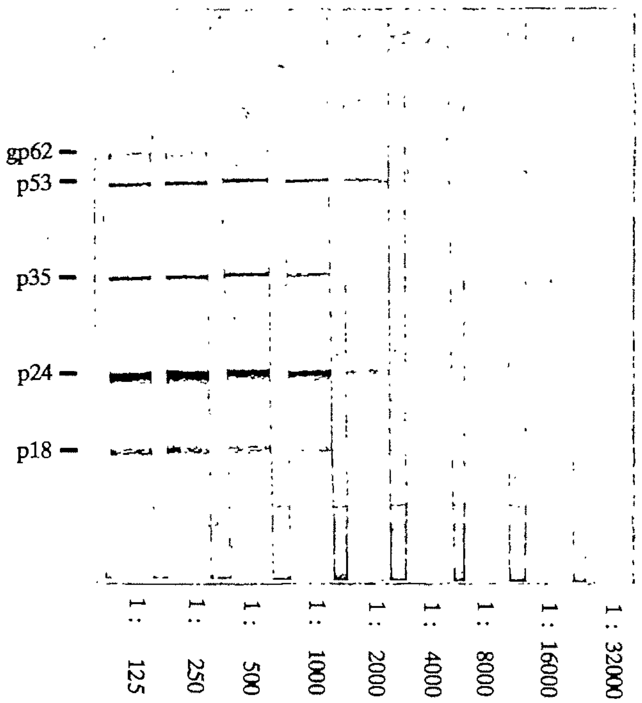

FIG. 5. Western blot from serum of *Case 5*. Titres and major HTLV1 antibody components indicated.

and asymptomatic relatives on the pseudotype neutralization assay (mean titre 1 : 15 000 v 1 : 10 000, $P < 0.028$), although there was a trend in the other groups.

Magnetic resonance imaging (*Table 3*)

Since abnormal signal from the white matter is present in at least 30% of apparently normal subjects over the age of 50 yrs it is important to consider the patients separately above and below this age. In this series there were only 4 patients less than 50 yrs old. All showed abnormal periventricular signal increased on T2 (fig. 6A–D) and decreased on T1 weighted sequences; there were also sparse foci of similar signal from the supratentorial white matter (fig. 6A) and, in 1, from the thalamus and right side of the pons (fig. 7A, B). In 1 patient there was incidental hypoplasia of the right cerebellar hemisphere.

There were 12 patients in the older group. Three had completely normal scans. The others showed (fig. 8A–D) altered periventricular signal (9), nodular altered signal in the supratentorial white matter (7), corpus striatum (2) and brainstem (1). The changes in 4 of these patients were slight (fig. 8C, D) and, with 4 exceptions, the periventricular abnormalities were no more than might be seen in apparently normal elderly people.

Scans from the 3 patients, born in the Caribbean but now resident in the UK, who had clinically definite MS were analysed for comparison with TSP. None of these

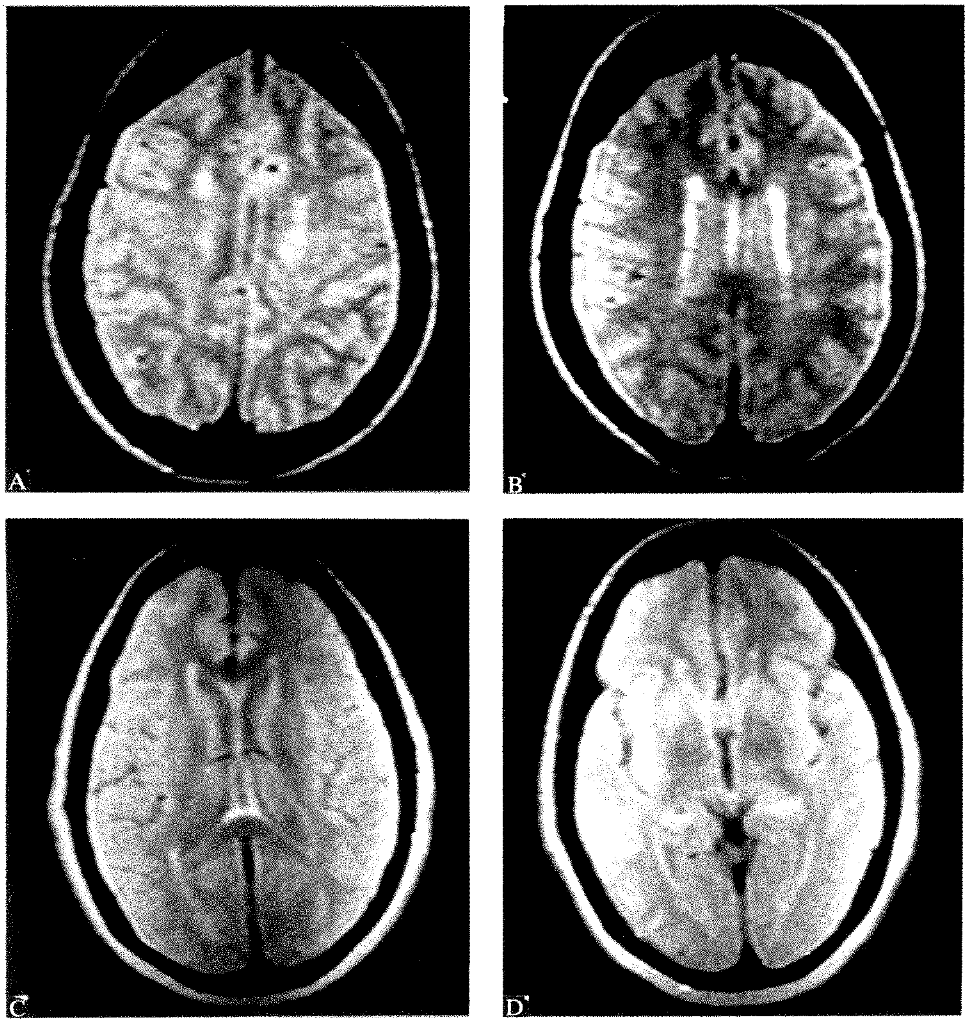

FIG. 6. MRI demonstrating cerebral hemisphere lesions in TSP patients less than 50 yrs of age. A, B. *Case 15* (SE 2 000/60) showing abnormally thick band of high signal around lateral ventricle and further high signal in right frontal white matter. C, D, *Case 9* (SE 2 000/60) showing periventricular high signal is slightly thicker than normal.

patients had antibodies to HTLV1. Regions of altered signal in the supratentorial white matter and brainstem were more frequent and extensive (fig. 9A, B). Periventricular altered signal was prominent in 2, and showed irregular extension into the deep white matter. This was not a feature of TSP where the signal change tended to form an even layer which could involve the corpus callosum, septum and body of the fornices.

The signal return from the spinal cord was normal in the 11 patients examined. There was focal atrophy of the thoracic cord in one. Protrusion of the C4/5 and/or C5/6 disc extended into contact with, and caused mild compression of, the spinal cord in 4 patients (fig. 10A, B). It was considered to be potentially relevant to the

TABLE 3. MAGNETIC RESONANCE FINDINGS

Case no.	*Cord*	*Brainstem*	*Corpus striatum*	*Peri-ventricular*	*Supra-tentorial*	*Other*
TSP						
1	N	N	N	N	N	Spondylosis
2	0	N	N	N	N	
3	Atrophy (T) N (C)	N	N	N	N	
4	N	N	N	+	+	
6	0	N	N	+ +	+	
7	N (C)	N	N	+	+	
9	DP C5/6*, C4/5* N (T)	N	N	+	N	Hypoplasia/atrophy R cerebellar hemisphere
10	DP C5/6*	N	N	+	+	
11	0	N	N	N	+	
14	N	N	N	+	+	
15	0	+	+	+ +	+	
16	N (C)	N	N	+	N	
17	0	N	+	+	+	
18	DP C4/5*	N	N	+	+	
20	N (C, T)	+	+	+ +	+	
21	DP C4/5*, C5/6	N	N	+	+	Spondylosis
MS						
1	0	+	+	+ +	+	
2	0	+	N	+	+	
3	+ (C)	+	N	+	+	

C = cervical; T = thoracic; N = normal; 0 = not examined; + = mildly abnormal; + + = moderately abnormal; DP = disc protrusion; * = with spinal cord compression.

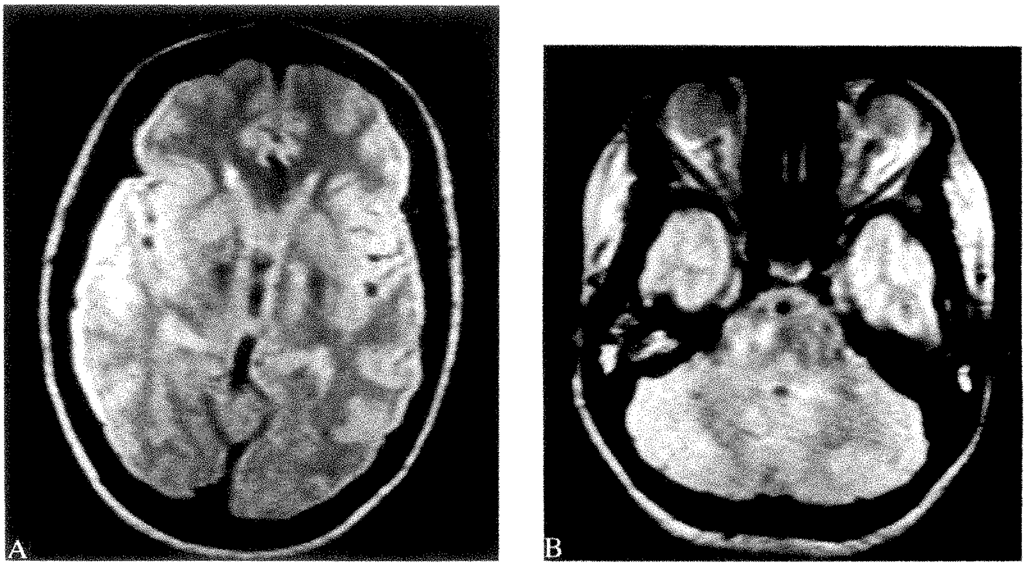

FIG. 7. MRI (SE 2 000/60) from TSP *Case 15* demonstrating regions of high signal in left thalamus (A) and pons (B). Such brainstem involvement was exceptional in TSP.

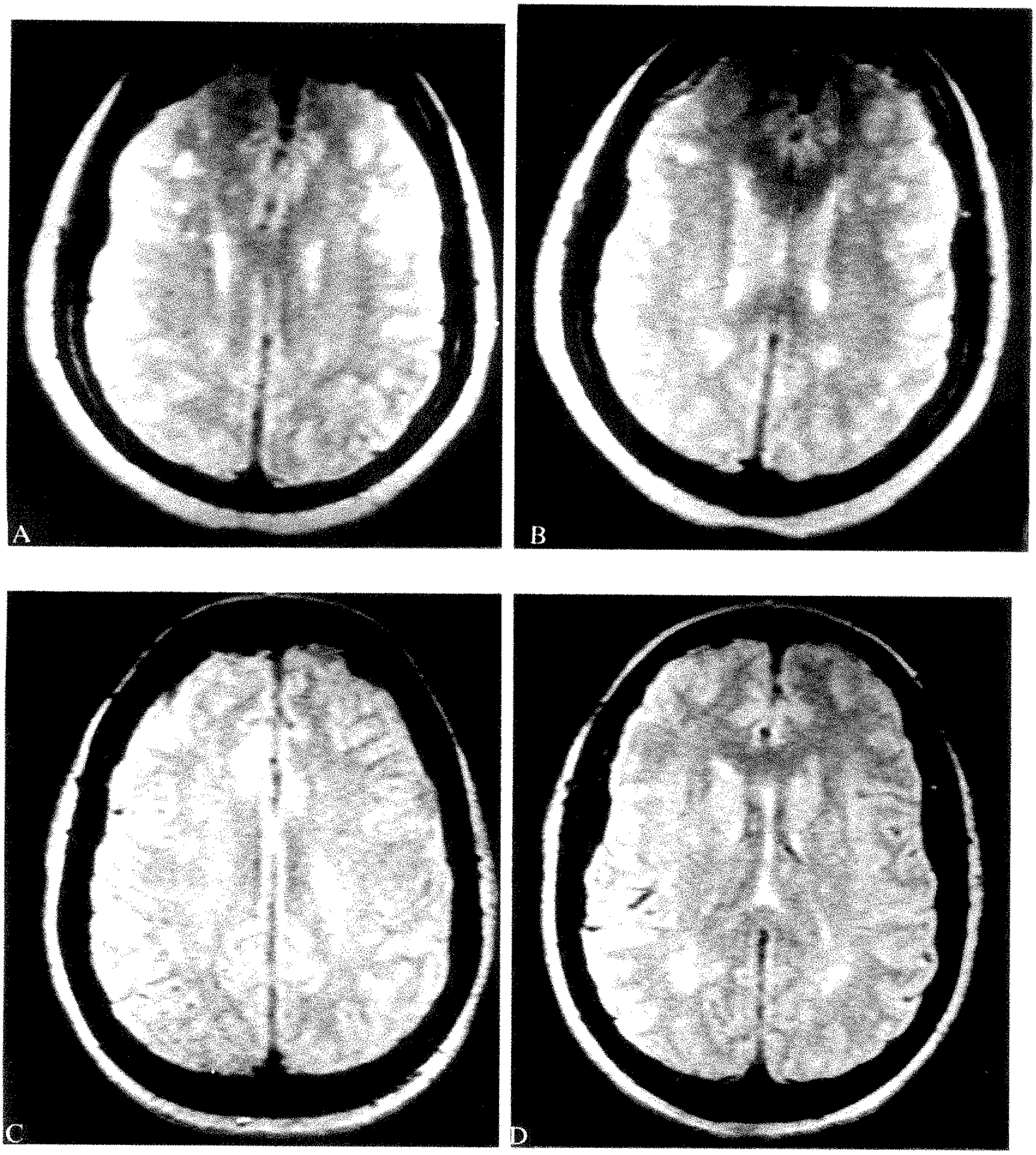

FIG. 8. MRI demonstrating cerebral hemisphere lesions in TSP patients older than 50 yrs. A, B, *Case 6* (SE 2 000/60), showing multiple areas of altered signal in the white matter of both hemispheres. C, D, *Case 21* (SE 2 000/60) showing multiple small high signal lesions in white matter of both hemispheres. The largest are adjacent to the lateral ventricles in peritrigonal regions.

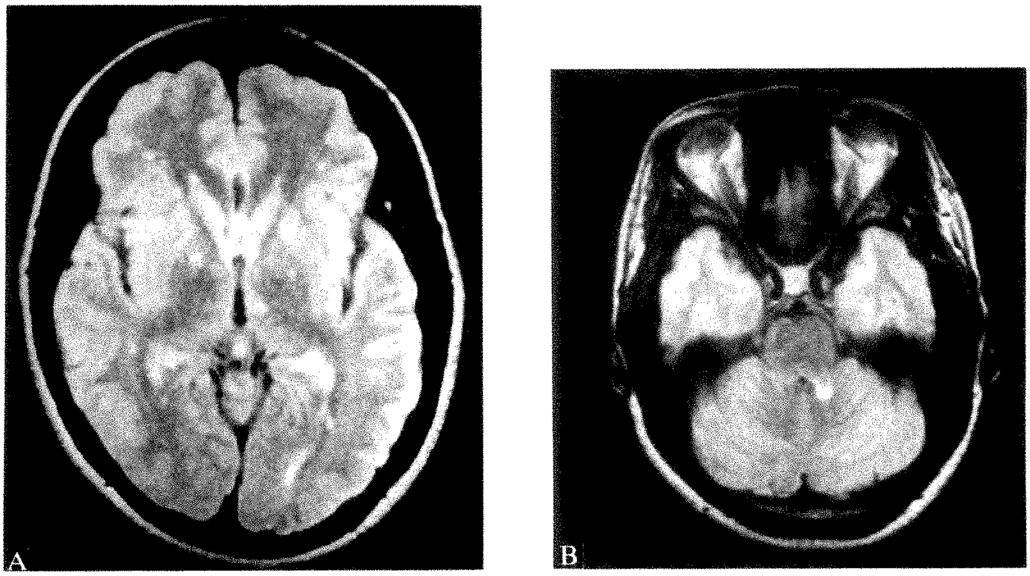

FIG. 9. MRI (SE 2000/60) of cerebral hemispheres (A) and posterior fossa (B) of patient with MS (*Case 1*) showing foci of increased signal in cerebral white matter, internal capsule and left middle cerebellar peduncle.

clinical abnormalities in only 1 of these patients but no improvement was obtained from surgery. The cord was examined in 1 of the patients with MS; there was swelling of the cervical segment within which there was an area of high signal consistent with demyelination (fig. 10C).

Review of previous pathology

The pathological findings in 11 cases of TSP were detailed by Montgomery *et al.* (1964). The microscopical slides from all these cases were reviewed for the present study. Although we do not know if any of the patients had antibodies to HTLV1, and repeated attempts to demonstrate antigen within the paraffin blocks have so far been unsuccessful, the clinical features of these patients documented by the original authors and those in the current study were sufficiently similar, if not identical, to suggest that both groups had the same condition.

The essential features common to all the cases are those of chronic meningomyelitis of the spinal cord, with involvement of long tracts (fig. 11), meninges, nerve roots, grey and white matter and very much rarer and milder involvement of the brain. The degree of involvement and the chronicity of the process vary considerably from one case to another. The more severely affected (e.g., Case 5 of the Montgomery *et al.*, 1964 series) show a florid picture of leptomeningeal lymphocytic infiltration extending along the perivascular spaces and widespread perivascular cuffing in the cord substance (fig. 12). All parts of the cord are affected, including the anterior horns of the grey matter, and often the intensely inflamed cord has

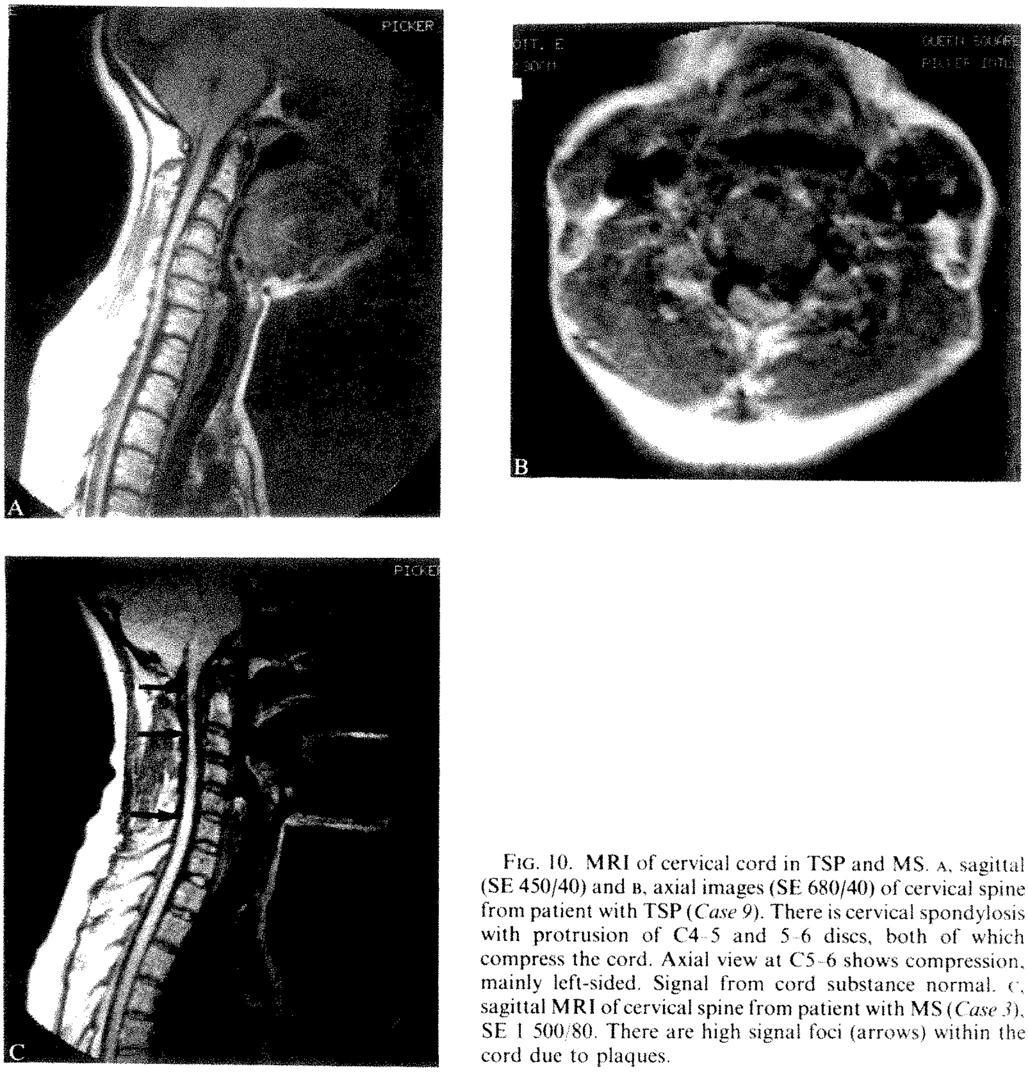

FIG. 10. MRI of cervical cord in TSP and MS. A, sagittal (SE 450/40) and B, axial images (SE 680/40) of cervical spine from patient with TSP (*Case 9*). There is cervical spondylosis with protrusion of C4–5 and 5–6 discs, both of which compress the cord. Axial view at C5–6 shows compression, mainly left-sided. Signal from cord substance normal. C, sagittal MRI of cervical spine from patient with MS (*Case 3*), SE 1 500/80. There are high signal foci (arrows) within the cord due to plaques.

undergone rarefaction and cystic necrosis in some small foci. Large fibrillary astrocytes are conspicuous in these regions (fig. 13), together with active microglia, macrophages and lymphocytes. Myelin sheaths are commonly broken and axonal destruction is evident, together with bulbous swollen axons (fig. 14). Reduction in the number of anterior horn neurons is obvious in the severe cases, but in all cases the changes of chromatolysis and of excess of lipochrome pigment may be seen. The sensory neurons of Clarke's column are frequently damaged.

Where there is heavy lymphocytic meningeal involvement, the anterior and posterior spinal roots are affected and become matted together with proliferating collagen fibres and inflammatory exudate. The anterior sulcus may be obliterated. Small arterial branches in the meninges are commonly thickened, but endarteritis is

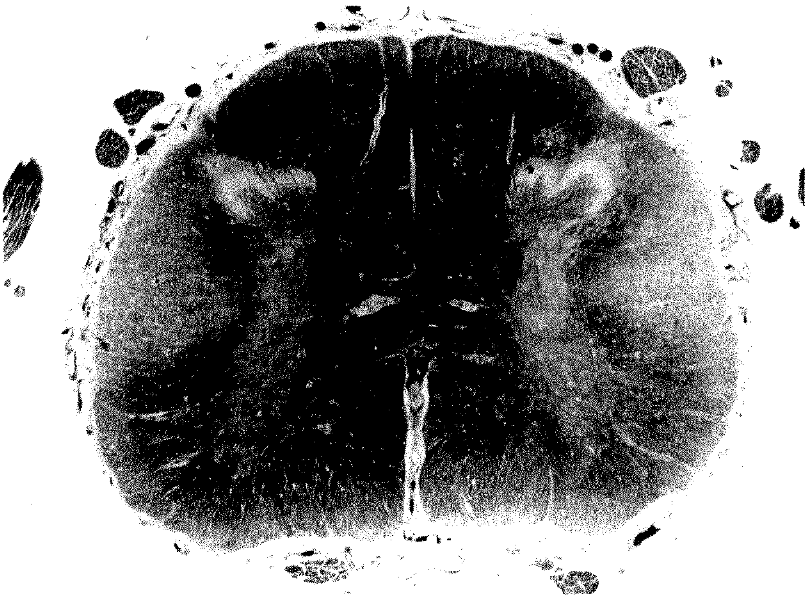

FIG. 11. Lumbar cord (L1). There is pallor of the pyramidal tracts but the posterior columns are within normal range. Celloidin, Heidenhain's myelin stain, ×6.5 (from *Brain* (1964) **87**, 464, plate LXXIV, fig. 2).

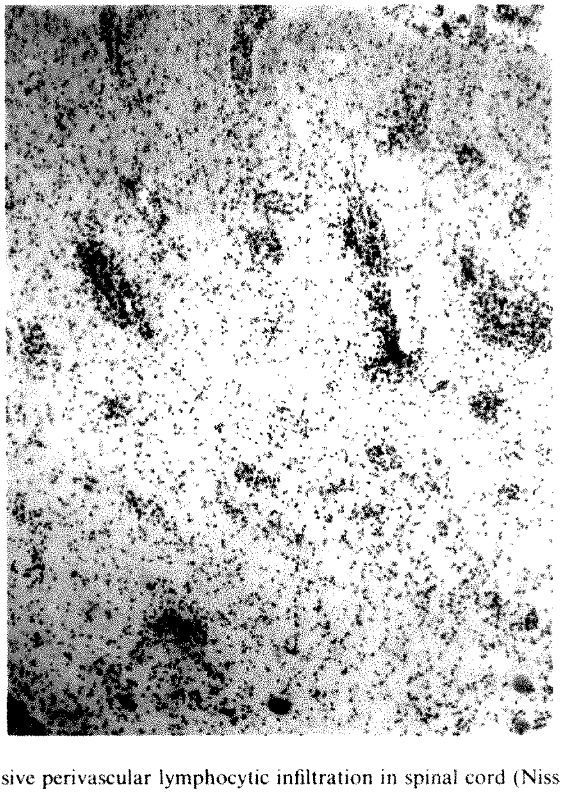

FIG. 12. Extensive perivascular lymphocytic infiltration in spinal cord (Nissl stain, × 160).

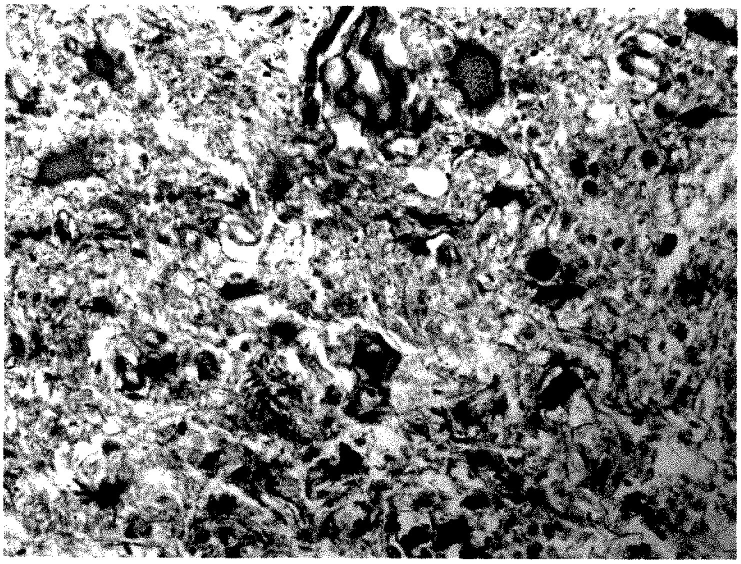

FIG. 13. Large fibrillary astrocytes in gliotic cord (PTAH, ×400).

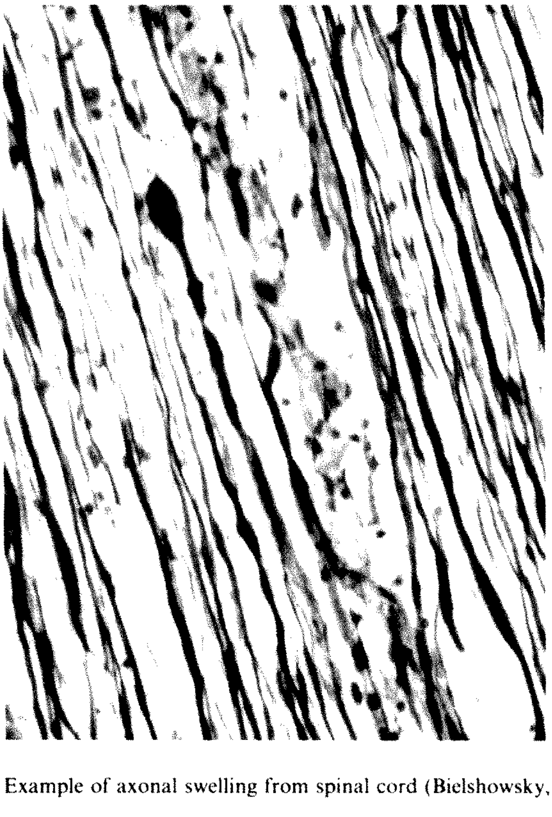

FIG. 14. Example of axonal swelling from spinal cord (Bielshowsky, ×540).

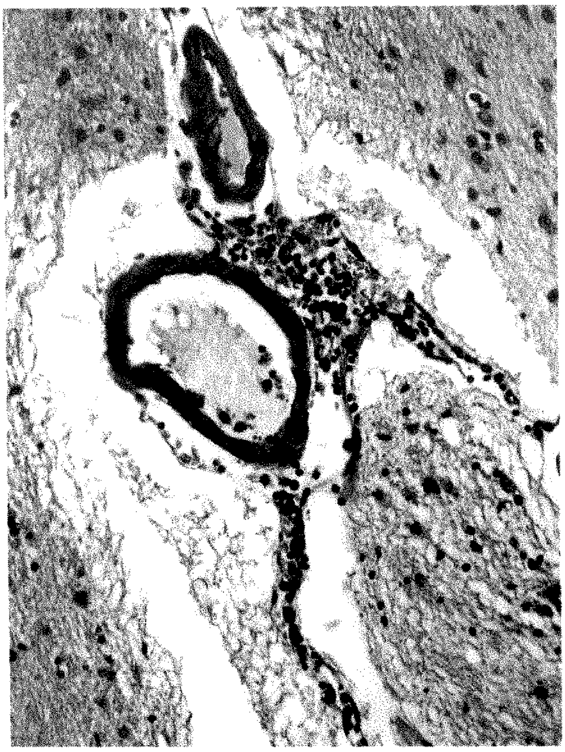

FIG. 15. Mild perivascular lymphocytic infiltration within spinal cord (haematoxylin-eosin, × 200).

not seen. In the milder chronic cases meningeal fibrosis, with some sparse lymphocytic infiltration, are found (fig. 15), even if the cord substance is largely spared.

The long tracts of the cord are frequently involved, but the pattern seen in sections stained for myelin varies from one case to another. It is not possible to determine, in these old optical microscope sections, whether the demyelination is primary or secondary, although there does appear to be relative sparing of the axons, suggesting that some of the pathology represents primary myelin loss. The lateral corticospinal tracts are the most commonly affected, then the posterior columns, especially the gracile fasciculi, and the spinocerebellar tracts. Pallor of myelin staining around the periphery of the cord is also common. Loss of myelin in the nerve roots is proportional to the degree of inflammation and fibrosis. Reduction of the myelinated fibres of the optic nerve may also be found.

External appearances of the brains were reported as normal apart from the leptomeningeal thickening, usually basal in distribution. Microscopically, foci of lymphocytic meningeal thickening are much less common than in the cord and perivascular accumulations of lymphocytes may rarely be found in the brain substance, both in the cortex and brainstem.

Asymptomatic relatives

We tested relatives of 11 of our TSP patients from Jamaica for HTLV1 antibodies. Of 69 living at the time of the study, 64 were contacted and blood was obtained from 60. They fell into three categories: those born and resident in Jamaica (group 1, mean age 52 yrs), Jamaican born, now resident in the UK (group 2, mean age 46 yrs) and UK-born offspring of the patients (group 3, mean age 20 yrs). No relative had TSP; 3 out of 25 (13%) from group 1, 7/21 (33%) from group 2 and 0/14 from group 3 were antibody positive on ELISA (χ^2 7.4, 2 df, $P < 0.02$). This contrasts with 4–6% positivity in unrelated subjects from the Caribbean resident in London. All relatives gave histories of being breast fed and none had received blood transfusions. Three of 7 spouses examined were antibody positive. The titres on ELISA, particle agglutination and antibody-directed cell mediated cytotoxicity tests were significantly less than those in the patients (geometric mean titres on ELISA 1:2700 as against 1:46000).

The relatives of the remaining patients, who mainly came from other Caribbean islands, have not been studied. However 1 spouse died of leukaemia of unspecified type in London 10 yrs before this study.

DISCUSSION

Clinical features

The clinical features of the patients described in this paper are similar to those described in the original series (Montgomery *et al.*, 1964) comprising a myelopathy which is usually progressive and begins in the third to sixth decade. Pain is a prominent symptom at the onset and often persists. Lumbar and radicular pain in the lower limbs involving several roots occurs in the majority. Minor paraesthesiae and numbness, again in the lower limbs, are common. The frequency of these sensory symptoms contrasts with the paucity of sensory signs. The disabling feature of TSP is the inevitable and usually early development of a spastic paraparesis. This is insidious in onset; only 1 patient described the weakness as developing suddenly. Initially the weakness may be unilateral. Soon, however, a progressive paraparesis develops although about one-third of our patients have had periods of up to several years of apparent stability. Ultimately severe disability results, 90% of patients requiring at least some assistance to walk, with 50% confined to a wheelchair within 10 yrs. Improvement did not occur in any patient spontaneously but was seen in 3 who received immunosuppressive drugs. Significant involvement of the anterior horn cells was not common in our patients. Upper limb involvement was not prominent, comprising mild spasticity, hyperreflexia and in some distal weakness. Bladder function was affected in 80%, beginning early in the evolution of their disorder, and the 2 males had sexual dysfunction.

Of considerable interest was the preponderance of women in our series, a finding that contrasts with the original studies where the sex incidence was equal in the whole population, although there was a female excess in those with negative syphilitic serology. More recently there has been a suggestion that females are more frequently affected in the Caribbean, at least if they are HTLV1 positive (Morgan *et al.*, 1988; Rodgers-Johnson *et al.*, 1988), but as our patients were migrants, selective return of men is a potential source of bias.

Montgomery *et al.* (1964) found that 7% of their paraparetic patients had sensorineural hearing loss and 15% optic atrophy. Only 1 of our patients had hearing loss; it was unilateral and due to barotrauma. In 1 patient there was clinical evidence of optic pathway abnormality and that comprised only a defect of colour vision in one eye. Similarly none of the initial series of 6 patients from Japan had clinical signs of optic neuropathy (M. Osame, personal communication). However, evoked potentials in our series did show that the visual and auditory pathways were abnormal.

Neurophysiology

Evoked potentials provided evidence of subclinical abnormality within the visual and auditory pathways and confirm our original report (Newton *et al.*, 1987).

VEP abnormalities were present in 50% of patients, a somewhat higher proportion than that found in the small series of Bhagavati *et al.* (1988) but similar to the report of Gout *et al.* (1989); in Japan the VEPs are usually normal (Kakigi *et al.*, 1988). There was a marked symmetry of the abnormalities of VEP latencies (only 2 patients had a unilateral delay), reminiscent of the situation in that subgroup of patients with MS who have a chronic progressive paraparesis. The simplest explanation of this symmetry is in terms of repeated small, probably demyelinating, lesions within both optic nerves and there is certainly evidence of pathology in the specimens examined from the 1960s. An alternative explanation is that the pathological processes involve the post chiasmal pathways in a symmetric manner. This, however seems less likely since, in contrast to MS, there was little evidence either at autopsy or on MRI of postchiasmal lesions.

The abnormalities of the AEPs, confirming our previous findings (Newton *et al.*, 1987) and those of the recent series of Bhagavati *et al.* (1988) and Gout *et al.* (1989), were of small magnitude, comprising prolongation of various brainstem components with a normal component 1. These again presumably reflect minor pathology within the brainstem. The lack of hearing loss, except in the 1 case of barotrauma, is not surprising in view of the multiple decussations that occur within the brainstem auditory pathways and the poor correlation in MS between abnormalities of the AEP and auditory acuity (Robinson and Rudge, 1977). In contrast to these findings, auditory evoked potentials are normal in Japanese patients with HAM (Kakigi *et al.*, 1988).

The abnormalities of the lower limb SEPs is perhaps to be expected in view of the pathology within the posterior columns relaying information from the legs. Kakigi *et al.* (1988) have recently described essentially similar results, although none of their patients had absent cortical responses; these workers have shown that the abnormality is due to abnormal conduction within the CNS. Of greater interest were the SEP abnormalities from the upper limbs. There was little evidence of a peripheral defect as only 1 patient had an abnormal N9 component and in none was there an abnormality of the SAPs recorded peripherally, either in amplitude or maximal conduction velocity. However, these techniques are relatively insensitive to axonal degeneration and proximal demyelination, both of which occur at least at the time of death, in some cases. Pathological delays of the various components of the centrally-generated SEP were found but there was no uniform pattern. For example, in the cases illustrated, the bulk of the delay in 1 patient seemed to occur between N9 and N13 and in another between N13 and N20. Whether this reflects different sites of lesions is unknown. In addition to the pathological latency increases, many of the components were degraded, presumably as a result of lack of synchrony of volleys of impulses. Three other groups have studied upper limb SEPs in TSP. Arimura *et al.* (1987) and Kakigi *et al.* (1988) reported that in Japanese patients the SEPs are usually normal, while Gout *et al.* (1989), who studied a small series of Afro-Caribbean patients, obtained similar results to those reported here.

Peripheral nerve conduction has been studied by three other groups. The results obtained by Arimura *et al.* (1987) and Morgan *et al.* (1988) are comparable to ours in that sensory action potentials, motor conduction velocities and compound muscle action potentials were normal. In contrast, Bhagavati *et al.* (1988) reported reduction of the compound muscle action potential amplitude, modest slowing of the fastest motor fibres and abnormality of the sural SAPs in half of their patients, but details are too sketchy to analyse their results further. Both Arimura *et al.* (1987) and Bhagavati *et al.* (1988) also reported abnormalities of F wave latency; these were not studied in any of our patients.

In the EMG studies we found surprisingly little evidence, in view of the pathology, of a lower motor neuron component to the weakness. Only 2 patients had unequivocal evidence of denervation. However, even in those patients who did have denervation in the lower limbs there was a marked upper motor neuron component to the weakness in that the discharge rates of individual units was low. Chronic partial denervation has been found by other workers. Thus Arimura *et al.* (1987) found that 5 out of 6 of their patients with HAM had this in the lower limbs, and 2 of these also had similar changes in the arms. Evidence of chronic partial denervation was found in the lower limbs and paraspinal muscles in 1 out of 12 patients studied by Bhagavati *et al.* (1988). These variations presumably reflect the patient populations studied.

Magnetic resonance imaging

The appearance of the brain lesions in some of these patients are not of themselves specific. Taken out of context they would be consistent with MS although, in general, they are less extensive than would be expected in patients with similar disability due to that condition. Indeed the 3 MS patients of similar ethnic origin and place of residence to our TSP subjects had much more extensive change, including abnormalities in the posterior fossa, even though they were all below the age of 50 yrs. The lesions are also consistent with ischaemia due to small vessel disease, and in the older patients some of the abnormalities were probably of this origin. The relatively high incidence of abnormality, the degree and extent in some cases and, above all, the clinical context, combine to make vascular disease alone an unlikely explanation.

Intrinsic cervical cord lesions are usually shown by MRI; abnormalities were evident in the single patient with MS in whom the cord was examined and are common in Caucasians with MS, but none was shown in the patients with TSP. The thoracic cord presents greater technical problems, and it was imaged in only 3 cases in this series; again the signal from it was normal but there was nonspecific atrophy in 1 patient. The high incidence of disc protrusion and spondylosis is not unexpected in this age group. It can be virtually impossible to assess the significance of minor degrees of cervical cord compression, particularly in the presence of TSP, but it is of note that all our patients had normal myelograms previously. It may be reasonable to perform decompression but in the 1 patient here in whom this was done it was unhelpful.

Pathogenesis

HTLV1 infection has been invariably associated with TSP in our patients. Others have found a lower prevalence of HTLV1 infection in patients fulfilling the criteria of TSP (e.g., Gessain *et al.*, 1985; Román *et al.*, 1987; Bhagavati *et al.*, 1988). A number of possible factors account for this variation. First, serum storage, with freezing and unfreezing, could affect antibody tests. Thus in Jamaica in the first report only 16 of 24 stored sera were positive (Rodgers-Johnson *et al.*, 1985) but all 19 of the most recent patients studied have been antibody positive by ELISA methods (P. Rodgers-Johnson, personal communication). Secondly, patient selection methods may play a part. Thirdly, precision of the diagnosis could be important if some techniques to exclude other causes (e.g., detailed myelography for arachnoiditis; Rodgers and Cruickshank, 1962) have not been applied in full. Finally, more than one agent or aetiology may be involved in producing unexplained paraparesis. TSP remains a clinical diagnosis and it would not be surprising if all myelopathies of unknown origin included other causal factors. While worldwide the data provide overwhelming evidence of a close association between HTLV1 infection and TSP it is not certain that the former causes the latter. However, intuitively it is tempting to assume that this is the case.

Does the neurological disorder result from a direct attack by the retrovirus on cells within the central nervous system or is there a series of secondary events that culminate in the neurological damage? There are preliminary reports that cultured glial cells can be infected with HTLV1 (Kim *et al.*, 1988) and that particles reputed to be virions have been seen on electron microscopy in unspecified spinal cord cells from a patient with TSP (Liberski *et al.*, 1988). These observations are consistent with direct invasion of neural cells. The finding of HTLV1 antigen free in the CSF and blood (Bhagavati *et al.*, 1988) is strong evidence of viral activity but does not elucidate which cell types are infected. We favour an alternative hypothesis of pathogenesis.

From animal work (*see below*) there is evidence that retroviral infection can damage the CNS via an immune mechanism rather than direct viral attack. The intense inflammatory perivascular and meningeal infiltrate seen in TSP, the presence of IgG and IgM oligoclonal bands in the CSF some of which are directed against HTLV1 antigens (also reported for IgG by Ceroni *et al.*, 1988), the presence of IL2 receptors on the lymphocytes, the extremely high titres of antibodies directed against HTLV1, the observation of the efficacy of high dose steroid therapy in HAM (Osame *et al.*, 1987), also observed in the 3 patients treated in our series, are all consistent with an immune hypothesis of CNS damage in TSP. None is a sufficient argument. Of particular interest is the high titre of antibody detected by the antibody-directed cell mediated cytotoxicity test compared with that found in asymptomatic infected relatives and patients with ATL. It is tempting to argue that antibody directed cytotoxicity occurs in vivo and that only in those patients with sufficiently high titres of HTLV1 antibody is neural tissue attacked by activated (infected) lymphocytes and/or mononuclear cells. Although the high antibody titres may merely reflect high antigen load the trigger for this attack may well be host rather than virus dependent. Whether direct neural damage occurs from activated cytotoxic lymphocytes per se remains to be determined.

In this paper we have not considered the problem of whether the HTLV1 retrovirus in patients with TSP and those with ATL are the same. There is evidence suggesting that the retroviruses are identical. For example the convoluted nuclei of infected lymphocytes are found in both groups of patients (Dalgleish *et al.*, 1988). These cells in our TSP patients are recognized by monoclonal antibodies made against HTLV1 from ATL patients. Furthermore, HTLV1 from ATL patients does induce IL2 expression on lymphocytes as in our TSP patients. More direct evidence that the viruses are the same comes from the work of Yoshida *et al.* (1987) using restriction mapping, and the recent studies of Tsujimoto *et al.* (1988) showing that there is a greater than 97% homology between HTLV1 isolated from a HAM patient and the viruses from ATL subjects. However, there are preliminary data from our patients suggesting that there are up to 5 nucleotide substitutions in the reverse transcriptase of HTLV1 compared with the virus associated with ATL (Bangham *et al.*, 1988).

If, as the Japanese data suggest, the viruses are identical (i.e., there is no neurotropic variant), why do some patients develop ATL, others have TSP and some remain asymptomatic even though infected? Since we have suggested above that TSP is primarily an immune mediated disorder, it is possible that host factors control the putative immunological attack and thereby determine which infected individuals develop TSP. Indeed in Japan it has been proposed, on rather dubious statistical grounds in our opinion, that TSP shows MHC restriction that is different from ATL and normal subjects (Usuku *et al.*, 1988). We have previously shown that the immunological response to HTLV1 in ATL patients and asymptomatic relatives who are infected is significantly weaker than in the TSP by a variety of assays (Dalgleish *et al.*, 1988). These data are consistent with host factors determining the course of HTLV1 infection.

Acquisition of the infection

HTLV1 is endemic in many areas of the world where it primarily causes ATL, although HTLV1 antibodies have been detected in homosexual men at risk from acquired immune deficiency syndrome (AIDS) and in groups of drug addicts, notably in Naples (Italy) and some British cities (Tedder *et al.*, 1984). Large numbers of migrants from the Caribbean have come to the UK, particularly London, in the past 40 yrs. Many of these West Indian families are split between their countries of origin and the UK and this geographical difference provided an opportunity to study the effect of migration on HTLV1 infection. Our hypothesis was that acquisition of HTLV1 would be most frequent in relatives born, and still resident, in Jamaica, would occur less commonly in Jamaican-born but now UK resident relatives and least frequently in the UK-born relatives (exclusively offspring here). There was a striking increase in the incidence of HTLV1 infection in the asymptomatic relatives of cases if the relatives were born in the West Indies and this was independent of their present place of residence. In contrast, among offspring born in the UK the incidence of asymptomatic infection was low.

Superficially these data suggest that the virus is acquired in the Caribbean and not in the UK. However, the relatives born in the UK are a generation younger (children of TSP patients, average age 20 yrs) than most of those born in the West Indies (average age 46–52 yrs). From Japan it is known that acquisition of HTLV1 antibodies occurs early in life in an endemic area, then remains static until adulthood when more subjects acquire antibodies (Kajiyama *et al.*, 1986). In extensive epidemiological studies of HTLV1 antibody acquisition in that endemic area, these workers have shown that in children transmission occurs almost exclusively from mother to child; the father's antibody status appears to be irrelevant as far as transmission to his child is concerned. On the other hand, in adults there is a much greater risk of transmission of antigen from male spouses to the wife than the reverse, semen being the most likely vehicle. These data are consistent with a sexual mode of transmission in adult life and possibly by suckling in infancy. In addition, it has been clearly shown that blood transfusion of infected material was a potent cause of transmission in Japan (Sato and Okochi, 1986).

In our series, all patients were breast fed and none had had blood transfusions. Vertical transmission, i.e. from our index case mother to child prenatally or perinatally, seems most improbable provided it is assumed that the mother was infected at the time of childbirth. On the other hand sexual transmission is likely and it is noteworthy that the asymptomatic spouses of our 2 male patients both had antibodies to HTLV1, one in very high titre. Of 5 other partners of our female index TSP cases tested, only 1 is positive. Furthermore, none of the patients' children, all of whom were breast fed, had acquired HTLV1 antibodies, at least in the first 20 yrs of life (mean age of the cohort), the age at which increasing seroconversion begins in Japan. It is not possible to confirm or refute our hypothesis that the virus is acquired in the West Indies but our data are consistent with a very long incubation period of TSP comparable to that seen in animal retrovirus-induced neurological disease (*see below*) provided it is assumed that a few short trips to the West Indies for holidays by TSP patients or their relatives would not be enough time to acquire infection. More data are required to take this further.

Neuropathology

Montgomery *et al.* (1964) discussed in detail the differential pathological diagnosis of the changes outlined above. At that time the possibility that meningeal and vascular syphilis might contribute to the picture could not entirely be excluded, especially in view of the positive treponemal reactions in the blood recorded in a majority of patients. In retrospect it is now easier to emphasize distinguishing features: endarteritis is not found, no meningeal gummata can be seen, and plasma cells and eosinophilic leucocytes are infrequent. In summary, the pathological changes are of active chronic meningomyelitis chiefly involving the cord, a picture consistent with an immune attack upon the nervous system.

Retrovirus-induced neurological diseases of animals

Retrovirus-induced neurological disease in man has only recently been described (HIV1, HTLV1) but has been recognized for many years in animals. This list includes murine leukaemia virus myelopathy (Gardner, 1985), visna/maedi in sheep (Sigurdsson *et al.*, 1957), caprine arthritis encephalitis in goats (Narayan and Cork, 1985), and the myelopathy occasionally seen in horses with equine infectious anaemia (McClure *et al.*, 1982). There is evidence that there are others, associated, for example, with feline retroviruses and simian immune deficiency virus. All are associated with the lentiretrovirus subgroup of the retroviridae with the exception of the murine and feline leukaemia retroviruses, both of which belong to the oncoretroviridae. All these disorders have features of slow virus infections as described by Sigurdsson (1954*a*); indeed maedi was the one that led him to formulate the concept of such diseases.

Visna (= wasting) and maedi (= dyspnoea) was studied extensively in Iceland in the 1950s by Sigurdsson who suggested that the disease was due to a virus (Sigurdsson, 1954*b*), later shown to be a retrovirus (Lin and Thormar, 1970). The mode of transmission was unclear although the farming methods in which large flocks of sheep are housed indoors in communal pens at certain times of the year suggested that respiratory or oral transmission was likely (Sigurdsson, 1954*b*). Extensive experiments by De Boer *et al.* (1979) showed that vertical transmission via the placental route was unimportant; lambs removed from their dams at birth did not develop serological or clinical evidence of infection, whereas animals allowed to suckle for 10 h or more did acquire the virus in many cases. If the contact was prolonged, i.e., for months, a high proportion of the lambs became infected.

Animals experimentally infected by intracerebral inoculation are apparently healthy but at autopsy many show an inflammatory exudate throughout the CNS and meninges; necrosis is seen at sites of the most intense inflammation (Sigurdsson *et al.*, 1962; Pétursson *et al.*, 1978). The CSF shows pleocytosis, and free virus can be isolated from it and the blood during the initial stages of the disease (Pétursson *et al.*, 1976). After a few months the pleocytosis lessens, the viraemia abates and free virus is no longer present. However, virus can still be recovered from the mononuclear cells in the blood, CSF and CNS tissues. The loss of free virus is accompanied by the development of antibody in the CSF and blood and there is evidence of intrathecal antibody synthesis. Months to years after inoculation some animals develop a progressive paraparesis. These animals show both primary demyelination of the cord and brain (Georgsson *et al.*, 1982) and inflammatory perivascular and periventricular exudates, sometimes with necrosis, in the CNS and the meninges.

Caprine arthritis encephalitis virus is genetically similar to visna virus but is a distinct species. In young goats a progressive paraplegia occurs. Pathologically the lesions are similar to those of visna. Interestingly, in contrast to visna, there is no antibody response to the virus (Narayan and Cork, 1985).

Equine infectious anaemia virus in horses rarely causes an encephalomyelitis (McClure *et al.*, 1982). Typically the animals develop ataxia of the hindlimbs due to proprioceptive loss and there may be weakness and wasting of the pelvic musculature. Pathologically, there is an intense meningitis, together with ependymitis and perivascular infiltrates affecting the spinal cord accompanied by CSF pleocytosis.

Gardner *et al.* (1973) described paralysis in some wild Californian colonies of Old World mice (Mus musculus domesticus) infected with murine leukaemia virus. Subsequent studies (for review, *see* Gardner, 1987) showed that paralysis developed many months after suckling infected milk and that it was due primarily to a loss of anterior horn cells accompanied by spongiform change. There was no inflammatory response. About 2% of the paralysed animals developed a lymphoma of a pre-B cell type while many others had lymphoma alone. The animals were persistently viraemic after infection but were otherwise immunocompetent. Not all strains of murine leukaemia virus cause paralysis; this neurogenic property resides in the envelope gene of the virus (Rassart *et al.*, 1986). On the other hand, the genetic constitution of the host also plays a part in susceptibility to CNS damage, certain alleles ($Fv1^n$) and recessive genes being important.

Other retroviruses have been implicated in neurological disease in animals but their role is ill defined. Simian immune deficiency virus (SIV1) causes an immune paretic illness in macaques (SAIDS) similar to that caused by HIV1 in man (AIDS). Recently, neuropathological abnormalities have been described in juvenile animals inoculated with SIV1 (Ringler *et al.*, 1988; Sharer *et al.*, 1988). The animals have all been neurologically asymptomatic. Characteristically there is a perivascular infiltrate of macrophages with multinucleate giant cells in the white matter of the entire CNS and also in the meninges. Myelin pallor has been reported in some animals. Virus-like particles are seen in the macrophages. In cats, feline leukaemia virus (FeLV) has been associated with a paretic illness similar to that in mice infected with MuLV described above (Hardy *et al.*, 1985) and a distinct feline lymphotropic virus causing an immune deficiency syndrome is also said to be associated with neurological abnormalities (Pedersen *et al.*, 1987). Further work is needed before these associations are accepted.

Visna is the best understood retroviral neurological disease of animals. The mechanism of persistence of visna virus in sheep in the presence of antibody has been subject to intense investigation (Haase *et al.*, 1977; Brahic *et al.*, 1981). In vivo viral expression is restricted, only about 1 in 10 000 cells of the choroid plexus expressing viral antigens, but in vitro cultured cells are permissive, large numbers of copies of viral RNA being produced with many cells expressing viral antigens on their surface. It thus seems that in vivo the virus remains hidden from the animals' immune system. Recent work by Gendelman *et al.* (1985) has shown that the macrophage is the primary target of visna virus. Precursor monocytes contain proviral DNA but viral replication and expression does not occur until mature macrophages evolve. Once the virus is expressed in vivo appropriate antibody is produced which presumably limits the spread of the virus to other cells. However, because of antigenic drift strains of virus different from those initially inoculated can be isolated. These different strains will initially be able to avoid the immune surveillance generated by the original virus and can thus infect further cells.

The pathogenesis of the CNS lesions is unclear. Host factors undoubtedly play a part in that certain breeds of sheep are highly susceptible (e.g., Icelandic), and there is evidence that an immune mechanism is important. Immunosuppression reduces the number of inflammatory lesions in experimentally infected sheep without reducing viral titres in short term experiments (Nathanson *et al.*, 1976) and conversely injection of purified virus with Freund's adjuvant in infected animals enhances the CNS changes (Nathanson *et al.*, 1981). Further, it is known that the infection of macrophages induces the expression of Ia antigens (Kennedy *et al.*, 1985) and this results in recognition of infected cells by lymphocytes which then produce a unique interferon (Narayan *et al.*, 1985; Zink *et al.*, 1987). This interferon retards the maturation of monocytes to macrophages, thereby reducing viral development but at the same time enhancing the immune response by stimulating Ia expression in the macrophages. Such a mechanism explains the intense inflammatory response seen pathologically with restricted viral expression. However, the processes whereby these events lead to neural damage, including demyelination, is obscure.

Conclusions

All the animal retroviral neurological diseases discussed above have similarities to HTLV1 myelopathy in man. Symptomatic neurological disease developing many years after infection followed by an essentially progressive course, although there may be periods of relative quiescence, is typical of the disorders both in man and animals. Furthermore, a substantial proportion of those infected do not become symptomatic. Visna is perhaps the best model for HTLV1 associated myelopathy with its strikingly similar pathology, namely, a meningomyelitis with a mixture of primary and secondary demyelination and gliosis. However, it would be unwise to extend the comparison too far as there are obvious differences, not the least of which is that visna virus does not cause tumours, i.e., it belongs to the lentiretroviridae, while HTLV1 causes an aggressive leukaemia in man. In spite of this, it is likely that a clearer insight into the mechanisms of neurological diseases associated with retroviruses will come from studying such animal models.

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PRESERVED OBJECT RECOGNITION AND READING COMPREHENSION IN OPTIC APHASIA

by H. BRANCH COSLETT *and* ELEANOR M. SAFFRAN

(*From the Department of Neurology, Temple University School of Medicine, Philadelphia, USA*)

SUMMARY

Optic aphasia is characterized by the ability to name from description and palpation but an inability to name visually-presented objects. Although originally attributed to a disconnection of visual information from object names, optic aphasia is often considered to be a mild form of visual agnosia. We describe a patient with optic aphasia who could access semantic information relevant to objects he could not name and comprehend written words he could not read. These data suggest that, at least in certain cases, this visual modality-specific naming impairment may not be attributable to impaired visual recognition. We suggest that this patient's preserved object recognition and reading comprehension was mediated by a semantic system supported by the right hemisphere.

INTRODUCTION

In 1889, Freund described a patient with a right homonymous hemianopia who, although apparently able to recognize visually-presented objects, was unable to name them; the patient could, however, name objects from touch. He attributed this impairment to a disconnection between the preserved right occipital lobe and the left hemisphere speech areas and designated this disorder 'optic aphasia'. A number of additional cases were soon reported (*see* Spreen *et al.*, 1966). However, after a critical review of the cases published before 1900, Wolff (1904) concluded that since alternative explanations of the syndrome such as a generalized naming impairment or visual agnosia had not been excluded, the existence of the syndrome had not been definitively established. Similarly sceptical opinions were expressed by Goldstein (1906) and Kleist (1916).

More recently a number of investigators (Lhermitte and Beauvois, 1973; Riddoch and Humphreys, 1987) have convincingly demonstrated that the clinical syndrome of optic aphasia as described by Freund (1889) does exist; the interpretation of these deficits, however, remains controversial. Certain investigators, citing the frequently reported observations that these subjects use objects appropriately in a naturalistic context and can demonstrate the gesture appropriate to an object

Correspondence to: Dr H. Branch Coslett, Department of Neurology, Temple University Hospital, Broad and Ontario Streets, Philadelphia, PA 19140, USA.

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that they cannot name, have concluded that object recognition is preserved and that the impairment involves accessing the object's name (Larrabee *et al.*, 1985). Others have argued that optic aphasia is attributable to impaired object recognition, on the basis of longitudinal observations of patients whose deficit evolved from visual agnosia to optic aphasia. Bauer and Rubens (1985), for example, concluded that optic aphasia is best considered a mild form of visual agnosia.

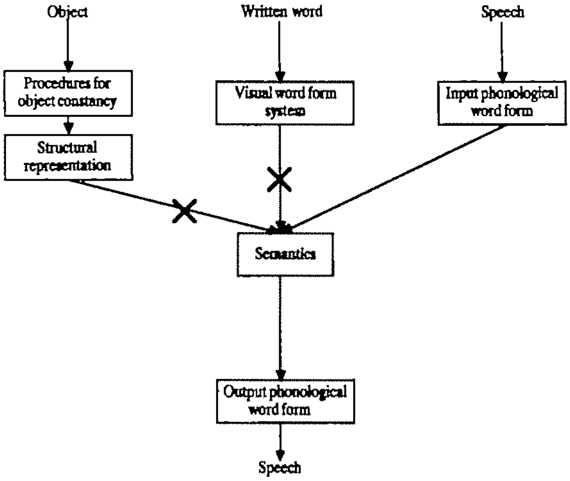

Object
Written word
Speech
Procedures for object constancy
Visual word form system
Input phonological word form
Structural representation
Semantics
Output phonological word form
Speech

FIG. 1. Schematic diagram of the processes involved in naming; the deficits thought by some investigators to cause optic aphasia are marked by **X**s.

Although optic aphasia is rare, the syndrome is interesting from a theoretical perspective because the interpretation of the visual modality-specific naming impairment has important implications for models of naming. Information processing accounts of object naming delineate a number of specific processes in the naming of visually-presented objects (*see* fig. 1). First, 'low-level' visual processes provide for the abstraction and integration of visual features such as shape, colour, texture and location. In order to access semantic information about the visual form thus generated, the computed image may first be compared with the individual's catalogue of stored visually-based object images or 'structural descriptions' which depict the visual attributes of the object. As object recognition is, for the most part, independent of the perspective of the viewer, a set of processes which provide for object constancy by permitting objects to be matched from different viewing perspectives must also be postulated. If the perceived visual form matches a stored structural description, semantic information appropriate to that object may be retrieved. Collectively, these processes provide access to semantic information, that is, object recognition. Object naming involves the additional procedure of activation of the auditory word form or output phonological address.

Many accounts of object naming assume that names may be accessed only after a complete semantic entry specifying general semantic category information as well as information about the object's function, attributes and associations has been accessed (e.g., Seymour, 1979; Warren and Morton, 1982). It is assumed, for example, that naming a hammer is dependent on access to information specifying (among other things) that the object is man-made, a tool, used for pounding, often made of metal and associated with nails. Additionally, many of the models (e.g., Warren and Morton, 1982; Snodgrass, 1984) assume that the semantic domain is modality-independent; that is, these models assume that the same semantic information will be accessed whether the object is visualized, touched or smelled.

Data from patients with optic aphasia are of interest because they present a serious challenge to these models. If, as has been argued since Freund's original report, the ability to produce a gesture appropriate for an object which cannot be named constitutes evidence of access to semantic information, then failure to name the object must be due to a breakdown not in the processes underlying recognition but in the mechanisms permitting the phonological form to be activated. If there is a single, modality-independent semantic system, however, object identification by palpation would be dependent on access to this same semantic entry and the naming of palpated objects should not differ from the naming of visually-presented objects; patients with optic aphasia are of interest, of course, precisely because they manifest this dissociation in naming.

A number of attempts have been made to account for optic aphasia. One suggestion made by Bauer and Rubens (1985) and more fully elaborated by Riddoch and Humphreys (1987) is that optic aphasia is characterized by an impairment in *access* to semantic information appropriate to visual stimuli. This account (*see* fig. 1) attributes the ability to provide the appropriate gesture for a visually-presented object either to access to information specified in an object's structural description or access to partial semantic information. In the former case, it might be argued that information represented at the level of the structural description of a hammer, for example, indicates that the 'handle' is the most appropriate portion of the object to grasp and that once having grasped a hammer in this manner, the types of gestures that might be produced are quite limited. For the latter, the ability to produce an appropriate gesture may reflect impaired access to or disruption of the semantic entry such that only partial semantic information may be available; thus, for example, on the basis of partial semantic access a visually-presented hammer might be categorized as a tool but additional semantic information may be unavailable. The constraints of the physical form of the object and partial semantic information may be sufficient to lead to the production of an appropriate gesture but insufficient to lead to the production of the name as this process is assumed to require a full semantic specification.

An alternative interpretation has been offered by Ratcliff and Newcombe (1982). These investigators postulated that names may be generated not only by a semantically mediated mechanism but also by a 'direct' mechanism which permits visually-presented objects to be named on the basis of stored visual images or structural descriptions without access to semantics (*see* fig. 2). As the semantically mediated mechanism is thought to be imprecise in that the same semantic entry may activate the phonological forms for 'hammer' and 'mallet', under normal conditions the direct mechanism is thought to augment the semantically mediated mechanism. On this proposal, optic aphasia is attributed to a disruption of the 'direct' mechanism which leaves subjects dependent on the imprecise semantically mediated mechanism.

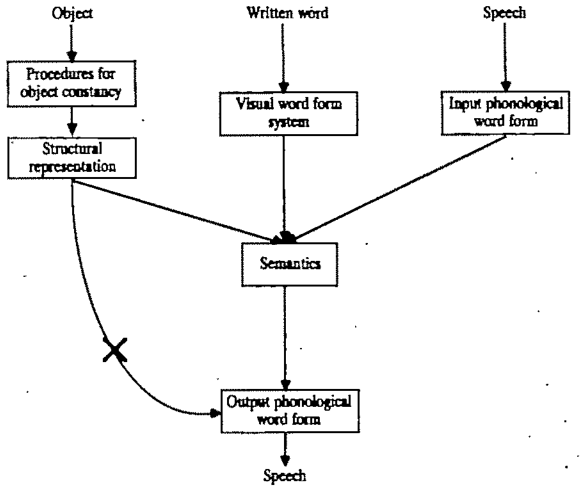

Object
Written word
Speech
Procedures for object constancy
Visual word form system
Input phonological word form
Structural representation
Semantics
Output phonological word form
Speech

FIG. 2. Schematic diagram of a naming model which incorporates a 'direct' naming mechanism.

A third proposal is that there are multiple, modality-specific semantic systems (Warrington, 1975; Beauvois, 1982; Beauvois and Saillant, 1985; Shallice, 1987). This theory, which is illustrated in fig. 3, proposes that semantic information relevant to all objects, words, concepts, memories, etc., is segregated according to the sensory modality in which that information is represented. For example, for the object 'hammer' there may be closely related but distinct entries in verbal, visual, and tactile semantic domains which would represent different types of information relevant to a hammer; the entry for 'hammer' in tactile semantics might contain information regarding weight, balance, and texture, the entry in visual semantics might contain visually-based information about object use and associated objects, and verbal semantics may contain verbally coded listings of associates, category membership, and attributes. On this account, modality-specific anomias are attributed to dissociations between the modality-specific semantic domains; more specifically, optic aphasia would be attributed to a disconnection between visual and verbal semantics. Thus the ability to demonstrate the appropriate gesture for an object is assumed to reflect access to the preserved

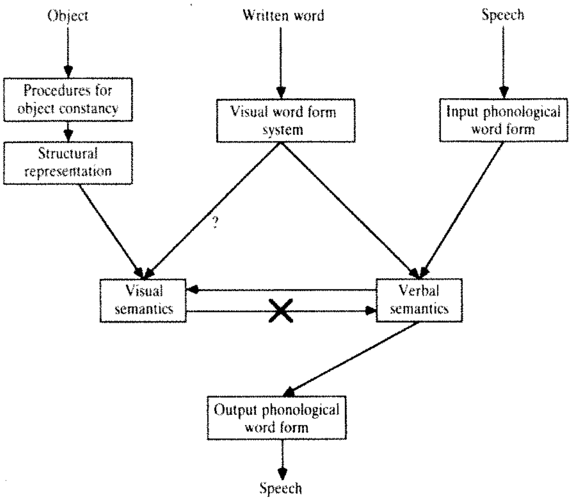

Object
Written word
Speech
Procedures for object constancy
Structural representation
Visual word form system
Input phonological word form
?
Visual semantics
Verbal semantics
Output phonological word form
Speech

FIG. 3. Schematic diagram of a naming model which incorporates distinct visual and verbal semantic systems.

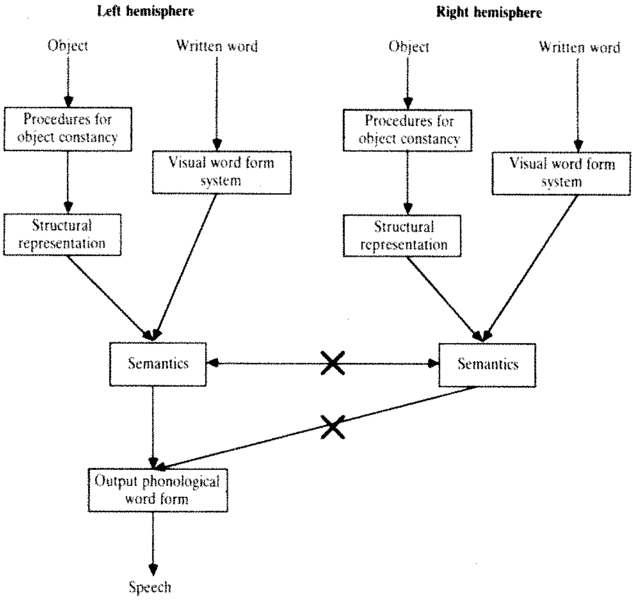

Left hemisphere
Right hemisphere
Object
Written word
Object
Written word
Procedures for object constancy
Visual word form system
Procedures for object constancy
Visual word form system
Structural representation
Structural representation
Semantics
Semantics
Output phonological word form
Speech

FIG. 4. Schematic diagram of a naming model which incorporates right and left hemisphere semantic systems.

nonverbal semantic entry; the failure to name the object is attributed to an inability to access the entry in verbal semantics and, consequently, to activate the phonological word form.

A final possibility is that patients with optic aphasia access right hemisphere semantic information but are unable to access the semantic system and speech production mechanisms of the left hemisphere (*see* fig. 4). This hypothesis, which is consistent with Freund's original account of optic aphasia, is similar to the previously discussed theory in that multiple semantic systems are proposed; however, in this account the semantic systems are presumed to be differentiated not by the modality of the information represented, but by the anatomical structures supporting the semantic systems.

We report a patient with optic aphasia whose performance on a variety of tests of object and word recognition helps adjudicate among the hypotheses described above. This patient was able to access semantic information not only for objects but also for words which he could not name. We believe that these data support the hypothesis that, at least for some patients, optic aphasia is attributable to a disconnection of the right hemisphere semantic system from the left hemisphere semantic and speech mechanisms.

CASE REPORT

The patient was a right-handed 67-yr-old male labourer with an eleventh grade education who noticed the sudden onset of confusion and right-sided weakness. He also stated that he could not see clearly and was noted by family members to bump into stationary objects on his right. His past medical history was significant for a mild left hemiparesis which lasted for approximately 1 month and resolved 2 yrs before his admission. The clinical diagnosis on admission was a left occipital lobe ischaemic infarction.

When first examined by the authors 24 days after admission, the patient was noted to be alert and cooperative but orientated only to person and place. The general neurological examination revealed a dense right homonymous hemianopia as well as a minimal spastic hemiparesis on the left and a mild spastic hemiparesis on the right. He exhibited mild pyramidal clumsiness of the left hand and severe clumsiness of the right hand. He also demonstrated optic ataxia with the right hand. Sensory examination was normal. The tendon reflexes were brisk bilaterally with a right-sided preponderance. No cerebellar deficit was noted. His gait indicated bilateral leg spasticity, greater on the right, where the plantar response was extensor.

A bedside evaluation revealed the patient's speech to be fluent and well articulated with normal prosody and information content. Auditory comprehension and repetition were normal. He was unable to name any objects with visual presentation but with palpation named most of the objects which he had been unable to name with visual presentation.

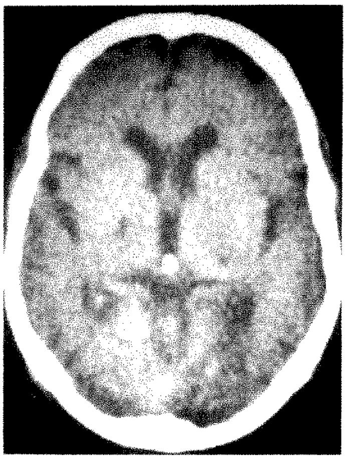
A CT scan performed 3 weeks after the stroke revealed left occipital infarction with involvement of the left forceps major and extension into the posterior limb of the internal capsule; a lacune in the posterior limb of the internal capsule on the right was also visualized (*see* figs 5, 6).

To assess further the patient's apparent modality-specific naming impairment, a comprehensive neuropsychological examination was undertaken and a series of experimental investigations were performed. The data reported here were collected over a 1 yr period during which there was no apparent change in the patient's performance. Because the use of his right hand was impaired by a pyramidal clumsiness as well as optic ataxia, he used his left hand on tasks requiring a pointing response or object manipulation.

Neuropsychological evaluation

Language assessment

Formal language assessment with the Minnesota Test for Differential Diagnosis of Aphasia (Schuell, 1972) revealed no impairment on those tests of auditory comprehension requiring a verbal response; performance was perfect, for example, on tests of sentence and paragraph comprehension.



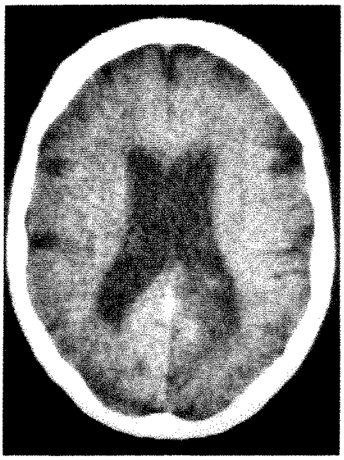


FIG. 5 (*left*). Low ventricular CT scan image demonstrating a large left occipital lobe infarct and a lacunar infarct in the posterior limb of the internal capsule on the right.

FIG. 6 (*right*). Midventricular CT scan image demonstrating an infarct of the left occipital lobe.

A mild impairment was noted in tasks in which the patient was required to point to or manipulate named pictures or objects. Repetition of words and sentences was perfect. Speech production as assessed by tests of automatized sequences (e.g., days of the week), responsive naming and elicited sentence production was normal. He correctly spelled aloud 10 of 10 words of 4 to 11 letters and correctly identified 10 of 12 words spelled aloud to him.

On a separate occasion, auditory comprehension at the single word level was tested by asking the patient to point to 1 of 4 named objects; the objects used in the Naming subtest of the Western Aphasia Battery (Kertesz, 1979) served as stimuli. He correctly pointed to 19 of 20 objects (95%).

Naming

Naming of pictures and visually-presented objects was grossly impaired. He failed to name correctly a single item in the naming subtest of the Boston Diagnostic Aphasia Examination (Goodglass and Kaplan, 1972); even when provided with semantic and phonemic cues, he correctly named only one item ('yoke') on the 60-item Boston Naming Test (Kaplan *et al.*, 1982). Finally, he failed to name any of 25 visually presented real objects.

Errors on the Boston Naming Test (Kaplan *et al.*, 1982) included 39 responses which bore no clear semantic, phonologic or visual relationship to the stimulus (e.g., scissors→'clock', volcano→'pillar'), 10 omissions, and 2 perseverations. Seven responses were semantically related to the stimulus; in 2 instances, the patient responded with names of supraordinate categories (e.g., cactus→'plant', beaver→'animal') and on 5 trials the patient made an associative error (e.g., trellis→'vines'). For only 1 item was there a suggestion of visually based error (stethoscope→'microphone'). There were no errors which bore a clear phonologic relationship to the stimulus.

Naming of palpated objects, in contrast, was quite good. With his eyes closed, the patient was able to name 23 of the 25 (92%) objects which he had been unable to name with visual input; a clear semantic relationship between stimulus and response was discernible in both of his errors (paperclip→'holds things together'; pipe→'cigarette, ashtray'). When asked to name the same objects by means of palpation but with his eyes open, the patient's performance deteriorated markedly.

The patient was also asked to name (or read) letters and words; he failed to name a letter correctly in 20 trials. He attempted to read aloud a corpus of more than 400 words in which the variables of part of speech, frequency, imagery and regularity of print-to-sound correspondences were systematically manipulated. He never correctly read aloud even a single word. Virtually all his errors were omissions. He repeatedly declined to offer any specific response other than to say 'I can't hardly see it'.

Lastly, the patient was asked to name 15 items from a verbal description (Coughlan and Warrington, 1978). He correctly named 11 items and recognized the other 4 items when given 4 names from which to choose.

Colour processing

Colour naming was assessed by asking the patient to name the colour of red, blue, green, yellow and orange 2 × 2 in coloured squares; the 5 coloured squares were presented individually; each square was presented 4 times. He correctly named the colour on only 4 (2 red, 2 yellow) of the 20 trials; this performance is not significantly better than chance. He responded 'yellow' or 'red' on 18 of the 20 trials.

The patient was also asked to point to a named colour patch in an array of 5 patches; each colour was tested 3 times. He failed on every trial. Errors appeared to be randomly distributed among the foils.

To determine if his poor performance was attributable to a loss of the concept of colour, 2 additional tasks were performed. First, he was asked to pick the appropriately coloured drawing from an array of 4 differently coloured drawings; for example, he was asked to pick the most 'natural' drawing of a tree from an array including trees with bright red, blue, yellow and green leaves. He was tested with a total of 8 different objects; he responded correctly on all 8 trials. Secondly, he was asked to provide the colour appropriate to 25 named objects (e.g., 'What colour is a lime?'). He responded correctly on 24 trials (96%)

Finally, his colour perception was assessed with the Ishihara colour plates (Ishihara, 1982). The patient was asked first to name and then to trace the numbers and trails on the Ishihara plates. Although he named only 2 of 10 numbers, he performed flawlessly on the tracing task, indicating that he perceived the colours.

Praxis

Praxis was initially assessed with the Florida Apraxia Screen (Gonzalez Rothi and Heilman, 1984) in which the subject is asked to demonstrate how a named object (e.g., 'key') is used. Profound pyramidal clumsiness prevented adequate testing of the right hand. With the left hand, the patient performed normally, producing an appropriate gesture to 13 of 15 commands. He made 2 'body part as object' errors. Comprehension of gesture also appeared to be normal; he correctly matched a gesture demonstrated by the examiner to 1 of 2 objects on 10 of 10 trials.

As an additional test of praxis as well as a preliminary test of visual object recognition, the patient was asked to produce the gesture appropriate to a visually-presented object; he produced the correct gesture on only 50% of trials. Despite repeated attempts to discourage him, during this task he consistently attempted to name the object before producing the gesture; in all instances, errors were appropriate to the patient's verbal response; when asked to produce the gesture appropriate to a visually presented key, for example, the subject responded 'knife' and produced the gesture appropriate for a knife.

Early visual processing

Although observations of the patient in a natural setting as well as the lack of apparent visually based errors on tests of naming argued against a significant impairment in early visual processing (or an 'apperceptive visual agnosia'), the possibility remained that the patient's impaired naming reflected at least in part an impairment of this type. To address this possibility, several tests of early visual function were performed. A test was administered in which the patient was shown two 12-

sided, black figures of approximately 3 × 4 in with irregular, complex contours and was asked to indicate if the figures were identical (LaBerge and Lawrence, 1957). The patient responded correctly on all 24 trials. The dot localization test (Warrington and Rabin, 1970) was also administered; he performed flawlessly on the 20 trials.

The patient's perfect performance on these tasks suggests that visual processes underlying form discrimination and comparison are preserved; a deficit in early visual routines would, therefore, appear to be an unlikely explanation for his modality-specific naming impairment.

PICTURE RECOGNITION

A series of investigations was undertaken to assess the patient's processing of nonverbal visual information.

Object-nonobject tests

The patient's ability to discriminate familiar objects from nonobjects was assessed with 2 forced-choice tasks. First, an object-nonobject test was performed. In this task 20 pairs of drawings were presented free-field to the patient; each pair included drawings of a familiar object and a nonobject. Stimuli were selected from those developed by Snodgrass and Vanderwart (1980) and Kroll and Potter (1984). The patient was asked to point to the familiar or real object; his performance was flawless (20/20).

On the second test, which was modelled after a test developed by Riddoch and Humphreys (1987), the patient was asked to discriminate drawings of real objects from nonobjects comprised of parts of real objects. Drawings of the real objects were from the Snodgrass and Vanderwart (1980) corpus and were taken from the following semantic domains: tools, animals, musical instruments, and household appliances. Thirty nonobject stimuli were constructed by making composites of 2 objects; all of the nonobject stimuli were generated by combining portions of 2 objects drawn from the same semantic category; for example, nonobjects included the head of a chicken on the body of a turtle and the head of a hammer mounted on the handle of a pair of pliers. Each drawing was individually presented for an unlimited period and the subject was simply asked to say 'yes' if the pictured item was familiar. The patient correctly rejected all nonobjects and correctly accepted 29 of 30 real objects. He erred with the drawing of a snail.

Data from these experiments are significant for several reasons. First, they provide additional evidence that the patient's inability to name objects was not attributable to poor visual acuity or an early visual processing impairment which might, for example, have prevented him from attending to or integrating visual information relevant to the object. Secondly, it should be noted that as the nonobjects in the second experiment were composites of the real objects used in that experiment, the patient could not have simply adopted a strategy based on the identification of single recognizable visual features such as the head of a chicken but was able to generate an integrated visual form. Thus these data suggest that the patient was able to access a set of stored representations for familiar objects.

Matching across view shifts

The recognition of a familiar object is, except under unusual circumstances, independent of the perspective from which it is viewed; normal subjects, for example, immediately recognize a bucket whether viewed from the side, top or bottom. Warrington and Taylor (1973) demonstrated that the capacity to recognize objects from unusual perspectives may be selectively impaired with brain damage; patients with right parietal lobe damage, in particular, may be able to name pictures of objects taken from a 'standard' perspective but unable to name pictures of the same objects taken from an unusual view, suggesting that in these patients the procedures that maintain object constancy are disrupted.

To determine whether our patient's impaired object naming might be attributable to impairment of these procedures, he was asked to match pictures of objects taken from a different perspective. Stimuli for this test included 3 pictures of each of 33 different objects; for each object, pictures were taken from 'standard' (that is, prototypical) 'familiar' (less typical but readily recognized) and 'odd' (unusual) views. The patient's task was to match each of the 99 pictures to the 'standard' view of the same object; for each of the 99 trials, the patient was given 1 of the stimulus pictures and asked to place the picture next to the picture of the same object on an answer sheet on which standard views of 3 visually similar objects (e.g., a pot, a trashcan and a round barbecue grill) were displayed. It should be noted that as the 'standard' views used for the answer sheet were identical to the 'standard' views used as stimuli, performance on the standard matching condition involved the matching of identical pictures.

The patient correctly matched all of the standard and familiar views and 29 of 33 of the 'odd' views. As most normal subjects perform errorlessly on this task, the patient may be slightly impaired in matching objects across view shifts. This mild impairment, however, cannot explain the patient's profound inability to name visually presented objects.

Categorization tasks

The previous investigations have suggested that the patient was able to use visual information to access perspective-free object representations. The next series of investigations, in which the patient was asked to sort pictures and drawings according to semantic criteria, was undertaken to determine if the patient could access *semantic* information relevant to the visual representations.

In the first test, the patient was asked to distinguish drawings of animals from other objects. Stimuli for the first test included 18 drawings of animals and 18 drawings of inanimate objects; pictures were drawn from the Boston Naming Test (Kaplan *et al.*, 1982) or the Snodgrass and Vanderwart (1980) corpus. Drawings were presented individually to the patient in a random sequence; he was asked not to attempt to name the stimulus but to place the drawings of animals in one pile and all other drawings in another pile. He performed the task flawlessly.

Secondly, the patient was asked to distinguish between drawings of edible and inedible objects. Stimuli for this task included 10 drawings of foods (e.g., an apple), 10 drawings of inedible objects which had no obvious semantic link to food (e.g., a hammer) and 10 drawings of items used in food preparation (e.g., pot, ladle). The semantically related foils were included to assess the specificity of the semantic information retrieved; impairment in semantic access or disruption of semantic networks might be expected to be associated with a confusion between items which are edible and items which are employed in the preparation of edible items. The patient was asked to sort the drawings as described above. He correctly sorted 29 of 30 items; he misclassified a drawing of a pot.

Finally, a categorization task was performed in which the patient was asked to match a photograph to another photograph of an exemplar from the same class of object. Stimuli for this test included pictures of each of 9 types of object. The 9 types of object were drawn from 3 semantic domains; the semantic domain of FURNITURE was represented by the exemplars 'chair', 'sofa' and 'lamp'; the domain of VEHICLES was represented by 'car', 'truck' and 'plane'; and the domain ANIMALS was represented by 'dog', 'cat' and 'fish'. For each type of object (e.g., 'car'), there were 7 photographs; 2 of the photographs were rated by controls as good examples of the item, 2 were rated as moderately good examples, and 2 were rated as unusual or bad examples; finally, a seventh picture was included which was identical to the exemplar on the answer sheet. On each of the 63 trials, the patient was given a photograph to match to an array containing the photograph of the 'standard' example of the stimulus item and the 'standard' photographs of the other 2 objects from the same semantic class; for example, on FURNITURE trials, the choices would be a prototypical chair, a prototypical sofa and a prototypical lamp. The patient was asked to place the stimulus photograph next to the appropriate photograph in the response set. The 63 stimulus photographs were divided into 7 blocks in which each of the 90 types of objects were represented;

the order of presentation was randomized within each block and the test was performed in two different sessions.

The patient correctly categorized 61 of 63 (97%) of the photographs; both errors occurred with photographs rated as bad examples (1 car, 1 sofa). This performance is within the normal range.

Thus the patient performed quite well on a variety of tests of picture categorization. One interpretation of these data is that the patient was able to access semantic information directly from visual information. Alternatively, it might be proposed that the visual information contained in the object images is sufficient to permit categorization of the drawings in the absence of full semantic specification, thus on this hypothesis, the ability to categorize a picture of a lion, for example, may reflect not the access to a full semantic entry indicating (in part) that the animal is a large carnivore which lives in Africa but to a generic 'animal' visual object representation which indicates that the object has a head, eyes, mouth and 4 extremities. (*see* Riddoch and Humphreys, 1987). In an effort to exclude the latter possibility, 2 additional experiments were performed in which correct sorting could not be performed on the basis of visual features alone but required access to object-specific semantic information.

Functional similarity

In the first test, which was modelled after the functional similarity test of Warrington and Taylor (1978), the patient was shown 3 pictures and asked to point to the 2 objects which were similar in function or 'served the same purpose'. As the stimuli were selected so that the functionally similar objects were visually dissimilar and the foil was judged to be more visually similar to one of the semantically related objects than was the other semantically related object, good performance on this task is not readily explained by the hypothesis that the subject categorized objects on the basis of basic visual features common to most members of a semantic category.

Stimuli for the task included 32 sets of 3 colour photographs. Two of the 3 objects were related in terms of function but were dissimilar in appearance while the foil was visually similar to one of the functionally related objects. Examples of the objects pictured in a trial included a zipper, button and coin and a coffee mug, wine glass and ceramic flower pot. The stimulus sheets were presented across a desk and no time limitation was imposed.

The patient was correct on 29 of 32 trials (91%); all 3 errors resulted from the selection of the 2 visually related stimuli. Normal controls 60 yrs and older scored from 27 to 31 correct with a mean of 30. Thus, the patient performed normally on this task.

The patient's normal performance on this task, together with the data from the semantic categorization tasks, indicates the he has access to semantic information appropriate to a visually presented object. Additionally, the ability to determine that visually dissimilar objects perform the same function suggests that he was not relying on information available at the level of a visual object representation or structural description.

Semantic association task

Many theories as to the organization of the semantic domain propose that semantic information is hierarchically represented (e.g., Warrington, 1975). It is postulated that superordinate information regarding, for example, the semantic class of a hammer (e.g., a tool) is accessed before subordinate (e.g., ball-peen vs. claw) or associative (e.g., often used with a nail) information. If this is true, it might be postulated that the patient is able to perform successfully the categorization and functional similarity tests described above by accessing only superordinate semantic information. As naming is thought to require access to a complete semantic entry, the inability to name the objects which were successfully classified might be attributed to an inability to access the full semantic entry.

To test this hypothesis, an experiment was performed in which the patient was required to group objects on the basis of semantic associations. In this experiment, 3 objects were placed before the subject and he was asked to indicate which 2 of the objects were associated or 'went together'; on the first trial, for example, a pencil, sheet of paper and knife were placed before the patient. A total of 15 trials were presented in a single session. He performed perfectly.

Collectively, the results of these investigations suggest that the patient's failure to name visually presented objects cannot be attributed to impaired early visual processing, failure to match visual information to stored structural descriptions or impaired access to semantic information. In particular, the normal performance on the funtional similarity and semantic association tests provide compelling evidence that he was able to access detailed semantic information relevant to visually-presented objects. Thus these data suggest that his naming impairments cannot be attributed to a failure of object recognition.

TESTS OF READING

The previous series of investigations attempted to demonstrate that the patient could indeed recognize objects that he could not name. The following tests were performed to determine if he could also process visually-presented verbal stimuli in the absence of explicit identification.

Because the patient never explicitly identified even a single word, a paradigm requiring the subject to make a choice among alternative responses was utilized for all of the reading tasks. This technique has been demonstrated to be effective in demonstrating reading capacities without explicit identification in normals (Marcel, 1983) and brain-damaged (Shallice and Saffran, 1986; Coslett and Saffran, 1989) subjects.

Lexical decision tests

First, a lexical decision test was performed; for this task, the patient was shown a series of 3 × 5 in white cards on which a single letter string had been printed in large (approximately 1.5 cm) lower case letters. The patient was told that it was not necessary to read the word aloud but only to say 'yes' if the letter string was a real word. No time limit was imposed. Stimuli included 41 real words of 5-7 letters with a frequency count of >250 per million in the Kučera and Francis (1967) corpus and 41 nonword letter strings (e.g., 'stete') derived from real words of >250 counts per million by changing a single letter.

The patient correctly accepted 88% of the real words and correctly rejected 66% of the nonwords for a score of 77% correct. Analysis with the d′ statistic reveals that this performance is significantly above chance ($d' = 1.59$, $z = 4.97$, $P < 0.01$).

Thus despite the patient's repeated explicit claim that he could not even 'see' the word, he nonetheless showed some ability to distinguish words from nonword letter strings. This finding suggests that, at least in most instances, he was able to perceive visually-presented letter strings correctly and to compare them to a catalogue of stored word forms. Thus his performance on this test, although far from normal, was substantially better than might have been expected given his total failure on oral reading tasks. In this respect, the patient's performance is similar to that of other recently reported patients with 'pure alexia' (Shallice and Saffran, 1986; Coslett and Saffran, 1989).

Normal subjects are sensitive to the appropriateness of the combination of word roots and endings (suffixes); normals, for example, consider 'tigers' to be a real word but recognize 'tigered' as an illegal combination and therefore, a nonword. To characterize further the patient's reading ability, a second lexical decision test was performed in which we examined his sensitivity to the legality of stem-affix combinations.

Stimuli for this study included 40 unsuffixed words (20 nouns, 20 verbs), 40 appropriately suffixed words (20 nouns, 20 verbs), 40 root morphemes with inappropriate suffixes (e.g., 'desking'), 20 unsuffixed nonwords and 20 suffixed nonwords. All root morphemes were greater than 100 counts per million (Kučera and Francis, 1967) and varied in length betwen 3 and 6 letters. The same suffixes were used for the appropriately and inappropriately suffixed root morphemes as well as for the suffixed nonwords. Nonwords were derived from high frequency (>100) root morphemes by changing a single letter. Stimuli were printed in large bold letters on a 3×5 in card and presented free-field without a time limit. The test was administered in two sessions.

The results, expressed as the percentage of stimuli the patient judged to be a real word, are expressed in the Table. Once again, he clearly discriminated between unaffixed words and nonwords. ($d' = 2.32$, $z = 6.18$, $P < 0.01$) Most significant in this context, however, was the finding that he accepted more inappropriately than appropriately suffixed words. Thus he was *insensitive* to the appropriateness of the combination of stem and affix.

TABLE. SUFFIXED WORD LEXICAL DECISION TEST (% 'YES' RESPONSES)

Unsuffixed word	93
Correctly suffixed word	63
Incorrectly suffixed word	68
Suffixed nonword	30
Unsuffixed nonword	20

Taken together, these results suggest that the patient was able to access a stored catalogue of words, one that was, however, limited with respect to providing information regarding affixation. Based on data from patients with pure alexia, we have argued elsewhere that these results are consistent with the hypothesis that performance was mediated by a right hemisphere lexicon (Coslett and Saffran, 1989).

Auditory word-to-print matching

Although the patient was totally unable to read aloud letters and words, the reason for this failure was not clear. One possibility was that he could derive the sound appropriate to visually-presented words but was unable to read the word aloud because of a disconnection between this stored phonologic information and speech production mechanism. To test this hypothesis, his capacity to access stored phonological information appropriate to visually-presented words was assessed by asking him to match an auditorily-presented word (or nonword) to 1 of 2 written letter strings.

Three experiments were performed; stimuli for the first experiment included 164 nouns of greater than 100 counts per million (Kučera and Francis, 1967) and varying in length from 4 to 7 letters. Stimuli for the second experiment included 80 functors of 4 to 7 letters in length and greater than 60 counts per million. Stimuli for the third experiment included 80 nonwords of 4 to 7 letters in length which were derived from words with a frequency of greater than 100 per million.

In all three experiments, 2 members of the same stimulus class (e.g. nouns) were printed in large, bold letters on a 3×5 in white card. The 2 words on each card were matched for length (in letters) and were judged by the examiners not to be visually similar; no pair of words shared the same initial letter or more than 50% of all letters. There was no clear semantic or phonologic similarity between the 2 words in each trial. Cards were presented free-field and no time limit was imposed. The patient was instructed to point to the word spoken by the examiner; spoken words were repeated approximately every 5s until he responded. Although he repeatedly stated that he could not 'see' the words and, in fact, *never* read a word aloud, he was encouraged to respond on every trial. He was not given feedback regarding the accuracy of his responses. Experiment 1 was performed in two sessions 1 wk apart; because of the relatively small number of trails in Experiment 2, the experiment was performed twice 2 wks apart. After only 10 trials in Experiment 3, he refused to continue, stating that the task was 'impossible'.

The patient responded correctly on 125 of 164 trials (76%) in Experiment 1; collapsing across the two administrations of Experiment 2, he responded correctly on only 89 of 160 trials (56%). Performance was significantly above chance on Experiment 1 ($\chi^2 = 45.1$, df = 1, $P<0.001$) but no better than chance on Experiments 2 ($\chi^2 = 2.03$, $P>0.10$) and 3.

The results of Experiments 1 and 2 indicate that the patient was able to access stored information relevant to nouns but not to functors. The fact that his ability to match spoken and written words was sensitive to lexical category argues against use of a phonologically based matching procedure, as does his total inability to perform the task with non-words. Clearly, his ability to match word tokens across modalities depends on access to lexical representations.

Written word comprehension

Finally, a series of written word comprehension tests was undertaken to determine if the patient could access semantic information relevant to written words.

In the first test, he was asked to match a written word to 1 of 2 pictures. The names of items pictured in the Boston Naming Test (Kaplan *et al.*, 1982) and Peabody Picture Vocabulary Test (Dunn, 1965) were used to create 31 pairs of words in which both words shared at least the first 2 letters (e.g., 'hand' and 'harp') and were matched for length or differed by no more than 2 letters. The 2 drawings appropriate to each pair of words were copied onto a single sheet of paper. Each of the 62 words was printed on a separate 3 × 5 in card and presented to the subject with the pair of drawings; the patient was instructed to point to the picture appropriate to the stimulus word. Each word was presented once; no feedback regarding response accuracy was provided.

The patient correctly matched the written word and picture on 47 of 62 trials (76%). This performance was significantly above chance ($\chi^2 = 16.52$, df = 1, $P < 0.001$).

A second test was performed in which the patient was asked to match a written word to 1 of 4 coloured drawings. The test was performed in two parts. In the first or 'Within Category' half of the test, words were tested against semantically related distractors; for example, for the stimulus word 'zebra', the pictured choices included ZEBRA, BEAR, BEAVER, and PORCUPINE. In the second or 'Across Category' portion, the same stimuli (e.g. 'zebra') were tested with unrelated distractors drawn from different semantic domains; in this portion, for example, the response sheet for the stimulus 'zebra' included pictures of a ZEBRA, PEAR, CLARINET, and DESK. There were 32 items on each part. The test was administered in four sessions and no stimulus was presented more than once per session. The task was also administered with auditory rather than visual word presentation. There was a 1 month interval between the auditory and written versions of the test.

With written stimuli, the patient correctly matched 22 of 32 (69%) words to the appropriate picture in the Within Category condition and 30 of 32 (94%) words to pictures in the Across Category condition. Performance was significantly better than chance in both conditions ($\chi^2 = 12.3$, df = 1, $P < 0.001$ and $\chi^2 = 31.4$, df = 1, $P < 0.001$ respectively).

With auditory stimuli, the patient correctly matched 28 of 32 (88%) of the Within Category and 32 of 32 (100%) of the Across Category stimuli. Once again, performance was significantly better than chance in both conditions.

Two additional tests were performed in which the patient was asked to sort written words into semantic categories. In the first task, he was asked to indicate if the referent of a written word was edible. Stimuli consisted of 25 food items (e.g., 'grape'), 25 words which were visually similar to the food names (e.g., 'graph') and 25 unrelated words. The three groups of stimuli were matched for frequency and length. Each of the 75 stimuli was printed on a 3 × 5 in card and presented to the subject across a desk for an unlimited time.

The patient correctly accepted 80% of the food names and correctly rejected 84% and 72% of the visual and unrelated foils respectively for an overall score of 79% correct. This performance was significantly above chance ($\chi^2 = 16.33$, df = 1, $P < 0.01$).

A second, quite similar task was performed in which the patient was asked to indicate if a written word was the name of an animal. Stimuli consisted of 25 animal names (e.g., 'mouse'), 25 visually similar words (e.g., 'mount') and 25 words which were visually and semantically unrelated to the animal names (e.g., 'rally'). The three types of stimuli were matched for frequency and length.

The patient correctly accepted 84% of the animal names and correctly rejected 76% and 84% of the visually similar and unrelated stimuli respectively for an overall score of 81%. This score was significantly above chance ($\chi^2 = 16.33$, df = 1, $P < 0.01$).

Thus, in a variety of tasks, the patient was able to derive semantic information from words which he could not explicitly identify and which he continued to insist he could not even 'see'. Additional investigations of his reading demonstrated that he performed better than chance on a lexical decision test with unaffixed words but was insensitive to the appropriateness of root and affix combinations. Finally, when asked to match an auditorily-presented word to 1 of 2 written words, he performed significantly better than chance with nouns but not functors.

DISCUSSION

The patient thus manifested the clinical syndrome of optic aphasia. He was unable to name visually-presented objects yet could name the same and other objects by palpation and from description. Unlike many patients with optic aphasia, he was unable to reliably demonstrate the use of objects he could not name by means of gesture, yet his performance on a variety of tasks of visual object processing and recognition demonstrated no impairment in access to semantic information appropriate to the objects he could not name.

Taken together, data from the object and word tasks have important implications for the competing accounts of optic aphasia outlined earlier. First these data argue against the hypothesis that optic aphasia is attributable to a mild form of object agnosia; the patient's normal performance on the semantic categorization and, in particular, functional similarity and object association tests suggests that he was able to use visual information to access a detailed semantic representation. Although these data do not unequivocally demonstrate that the patient had access to the *complete* semantic entry thought to be necessary for normal naming, it might be expected that the semantic information which supported his normal performance on the experimental tasks would be sufficient to permit him to generate *some*, perhaps less specific, response; for example, it might be expected that this information would be adequate to generate a nonspecific response such as 'tool' for the stimulus 'hammer'. Finally, as this hypothesis addresses only object naming it does not account for the associated and, in some respects, parallel impairment in reading demonstrated by our patient.

These data are not parsimoniously accommodated by the hypothesis that optic aphasia is attributable to a dissociation between distinct modality-specific visual and verbal semantic systems. This hypothesis predicts that the patient would be unable to associate visual and verbal input; that is, he would *not* be expected to be able to either name visually presented objects or point to named objects. Our patient, like other reported patients with optic aphasia, was, in fact, able to point to named objects (Larrabee *et al.*, 1985). To deal with this aspect of the data, it would be necessary to postulate a unidirectional impairment; that is, that the visual-verbal dissociation was specific to language production. It would also be necessary to posit an additional deficit to account for the parallel impairment in reading.

The patient's colour anomia may also be relevant in this context. Based at least in part on data from an elegant study of a patient (M.P.) with 'optic aphasia for colours' (Beauvois and Saillant, 1985), Beauvois (1982) concluded that optic aphasia is attributable to a dissociation between visual and verbal semantics. This claim was supported by the finding that M.P. performed well on tasks in which the stimulus, response and intervening processes were entirely verbal or entirely visual but performed poorly on tasks requiring access to both visual and verbal information. Although our patient and M.P. performed similarly on a number of tests, they differed in one important respect; our patient performed very well (96% correct) when asked to name an imagined object's colour (e.g., 'What colour is a lime?') whereas M.P. performed poorly. Although our patient's good performance might be attributed to the fact that information specifying the colour of an object is represented in a 'verbal' semantic store, this hypothesis would not account for M.P.'s poor performance on this task. Thus, as our patient performed well on a task presumed to require access to visual and verbal knowledge, his performance is not explained by the theory that verbal and visual semantic systems are dissociated.

The dual route hypothesis, which proposes that names may be generated not only by a semantically mediated mechanism but also by a 'direct' mechanism, also appears to be inconsistent with the patient's performance. The patient's complete failure to name visually presented stimuli suggests that both the 'direct' and semantically based mechanisms are disrupted; his good performance on the functional similarity and object association tasks, however, demonstrates that he could access detailed semantic information from visually-presented objects and, therefore, that the semantically based mechanism is at least relatively preserved. Furthermore, if he can access semantic information from visually presented stimuli, this hypothesis predicts that he would generate semantically based responses to visual stimuli. Although semantically based errors were noted, they were infrequent (6% of trials) and were far outnumbered by trials on which he claimed not even to have seen the stimulus. Additionally, if he accessed semantically based information but could not adequately specify the phonological form of the word, phonemic cues might be expected to improve performance; yet there was not one instance in which a phonemic cue led to a correct response. Finally, this hypothesis does not offer a principled account of his reading performance.

The final hypothesis to be considered is that the patient's performance with visually-presented stimuli was mediated by the right hemisphere. This hypothesis assumes that the relatively intact right hemisphere supports early visual processing, structural descriptions, procedures for matching across view shifts and a semantic system. It also assumes that, as a consequence of his left occipital infarct and resultant right homonymous hemianopia, all visual information initially accesses the right hemisphere and is prevented from accessing the left hemisphere speech mechanisms because of infarction of the fibres of the forceps major in the medial aspect of the left hemisphere. (Damasio and Damasio, 1983; Henderson *et al.*, 1985) Thus the processing of visual information (that is, to the point of access to semantics) in this patient is, therefore, assumed to be restricted to the right hemisphere.

We believe that this hypothesis may account for all our data. On this hypothesis, the patient's preserved ability to access semantic information relevant to visually-presented objects is attributable to the capacity of the right hemisphere to use visual information to access the right hemisphere semantic system; the failure to name visually-presented objects may be attributed to an inability to access the phonological output lexicon in the left hemisphere. This contention is supported by an analysis of the patient's naming errors which, for the most part, demonstrated no clear relationship to the stimulus; this pattern of naming errors is reminiscent of the profile observed in patients after corpus callosum transection in whom it is also assumed that there is a disconnection between the right hemisphere mechanisms underlying visual object recognition and the left hemisphere-mediated speech production mechanisms (Gazzaniga and Sperry, 1967). Additionally, the striking descrepancy between the patient's good performance on a variety of word and object recognition tasks and his explicit claim that he had not been able to 'see' the stimulus has been reported with patients following corpus callosum transection and has been interpreted as evidence that the left hemisphere language mechanisms are dissociated from processing operations carried out by the right hemisphere (Sperry *et al.*, 1969).

Another important line of evidence consistent with the right hemisphere hypothesis is that, unlike the other accounts outlined above which do not explicitly address the issue of word identification, this hypothesis predicts the pattern of reading performance demonstrated by the patient. A number of investigators, citing studies with normal subjects, investigations of patients after transection of the corpus callosum and studies of patients with acquired reading disorders such as 'deep' dyslexia (Saffran *et al.*, 1980; Coltheart, 1983) and pure alexia (Shallice and Saffran, 1986; Coslett and Saffran, 1989), have suggested that the right hemisphere has some reading capacity. The presumed right hemisphere language capacities are thought to differ in a number of important respects from those of the left hemisphere. It has been hypothesized, for example, that the right hemisphere does not support speech production mechanisms and that the putative right hemisphere lexicon consists primarily of major lexical items of high imagery; additionally, it has been suggested that the semantic errors (e.g., reading 'uncle' as 'cousin') characteristic of deep dyslexia reflect right hemisphere involvement in reading (Coltheart, 1983). Finally, Coslett and Saffran (1989), citing evidence from patients with 'pure alexia' who were insensitive to the appropriateness of root and affix combinations, have suggested that the right hemisphere does not adequately support processes involving affixation.

Additional support for the right hemisphere reading hypothesis comes from a recent report of a right-handed teenaged girl who underwent a left hemispherectomy at the age of 15 yrs (Patterson *et al.*, 1989). Subsequent to the hemispherectomy, the patient exhibited a reading impairment quite similar to deep dyslexic patients and split-brain patients given reading tests with stimuli restricted to the right hemisphere.

Our patient's performance was typical of that attributed to the right hemisphere in all respects. He was totally unable to read aloud but was able to derive meaning from visually-presented words; he was able to match auditorily-presented nouns but not functors or nonwords to written words, a finding consistent with the hypothesis that functors are poorly represented in the right hemisphere. He was insensitive to the appropriateness of affixes, a finding consistent with the hypothesis that the right hemisphere does not represent affixed words or the mechanisms for relating words roots and affixes. Lastly, although he did not make frequent semantic errors in oral reading tasks, the patient did make significantly more errors on the within-category as compared to across-category written word to picture matching task suggesting that he made 'semantic' errors in comprehension.

The hypothesis that this patient's optic aphasia was attributable to a dissociation between the right hemisphere visual processing mechanisms and the left hemisphere speech production mechanisms is, of course, quite similar to the disconnection account of pure alexia (Dejerine, 1892). In this context it should be noted that a number of recent investigations of patients with pure alexia have demonstrated that reading may be at least relatively preserved in this syndrome, often in the face of the patient's explicit statement to the contrary (Landis *et al.*, 1980; Marcel, 1983; Shallice and Saffran, 1986). It should be noted in this context that the pattern of impairments demonstrated by the pure alexics reported by Shallice and Saffran (1986) and Coslett and Saffran (1989) was quite similar to that manifested by our patient with optic aphasia. Thus these patients with pure alexia exhibited an insensitivity to the appropriateness of affixes, relatively preserved reading comprehension and better performance with nouns as opposed to functors. The patient with pure alexia reported by Shallice and Saffran (1986), in fact, also exhibited a mild form of optic aphasia.

Why a lesion which is presumed to disconnect the left hemisphere from visual information causes optic aphasia in some individuals and pure alexia in others is not clear. One possible explanation is that optic aphasia is associated with larger lesions. Geschwind (1965) proposed that the callosal fibres mediating object naming, which presumably originate in parietal association cortex, cross the corpus callosum more anteriorly than those interconnecting visual cortices which cross in the splenium. On this analysis, pure alexia would be expected to be caused by a lesion of the splenium or forceps major but optic aphasia would be caused by a larger lesion which would interrupt both the fibres interconnecting the visual cortices and perietal association cortex. Unfortunately, a comparison of the CT scans of our patient with optic aphasia and 4 patients with pure alexia does not support this hypothesis.

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BOOK REVIEWS

Contributions to Contemporary Neurology: A Tribute to Joseph Michael Foley. Edited by R. B. Daroff and J. P. Conomy. 1988. Pp. 259. Boston and London: Butterworths. Price £49.95.

This volume is an elegantly produced collection of papers published as a tribute to Dr Joseph Foley after his retirement as head of the Department of Neurology at Case Western Reserve in Cleveland. As the biographical sketches point out, however, he is of course by no means retired.

Dr Foley is a well-loved and highly respected figure in world neurology and has left his mark on many who were associated with him, initially at the Boston City Hospital and later in his long tenure of headship of the Department of Neurology in Cleveland. The early part of his career spanned a time of great expansion in neurology in the United States and he was one of its most successful guiding figures.

The range of contributions in this volume from his former colleagues is a wide one from Richard Johnson's chapter on AIDS and its neurological complications (ending incidentally with the gloomy reflection that more successful treatment of opportunistic infections in AIDS may lead to an increasing number of surviving but seriously damaged sufferers) to Simon Horenstein's classical paper on abnormalities of posture and movement following parietal lobe lesions. Recent techniques applied to old problems are represented, for example, by a study of head scanning in olivopontocerebellar atrophy.

It is invidious in a collection of this sort to select papers on their relative merits except by personal preference. In addition to the contributions already mentioned, the ones which I most enjoyed were Joseph Van der Meulen's thoughts on brain death and the important weight which is attached to the neurologist's opinion, Richard Chambers' account of a rarity in the form of a case of lymphocytic hypophysitis, and Betty Banker's observations on inflammatory muscle disease.

Taken together the collection fully reflects the great occasion on which the papers were delivered.

C. J. EARL

Brain Injury and Recovery. Theoretical and Controversial Issues. Edited by S. Finger, T. E. LeVere, C. R. Almli and D. G. Stein. 1988. Pp. 368. New York: Plenum Press. Price $69.50

Rehabilitation of the Severely Brain-Injured Adult: a Practical Approach. Edited by I. Fussey and G. M. Miles. 1988. Pp. 223. London: Croom Helm. Price £12.95 (paperback).

Brain Injury and Recovery examines theoretical issues such as the localization or distribution of functional systems; the functional dedication or equipotentiality of brain regions; and the restitution or substitution of function following injury. The editors 'recognize . . . that science is guided by new technologies, by hard data, and by theories and ideas'. This list is arranged in descending order of concreteness (note 'hard' data), as though theory were the least reputable of the three elements. New technologies and 'hard data' do suggest new experiments in a more or less random manner, but science and clinical practice are largely guided by theoretical programmes which are not necessarily explicit. The theory may be implicit, for example when the interpretation of the effects of brain injury is influenced by a hierarchical view of cortical function bearing the hallowed authority of Hughlings Jackson. As Feyerabend remarked, scientific evidence 'does not merely describe some objective state of affairs but also expresses . . . subjective, mythical and long-forgotten views'.

In a book concerning theory and controversy one would like to see such 'mythical and long-forgotten views' exposed to the light of day. There is a paper on Margaret Kennard, redressing some imbalances in her reputation for work on the increased capacity for recovery from injury to the developing brain. Another chapter effectively summarizes Hughlings Jackson's theory of localization and compensation. Other theorists such as von Monakow, Munk and Luria are not given separate treatment, but there is an especially attractive chapter on Goldstein, demonstrating that he was able to maintain an interest in classical neurological lesion-localization while developing a 'holistic' theory of brain function and recovery. The difficulty with all these essays is that they deal too reverently with the texts rather than analysing their contemporary relevance. The study of what Jackson, or Kennard, or Goldstein (or Freud, or Marx) 'really said' is of part historical, part antiquarian interest. A more important question, calling for greater historical and historiographical sophistication, is: 'What are Jackson, Goldstein, etc. . . . saying today?' Is their intellectual legacy (distorted or otherwise) to be found in the methods and results sections as well as in the historical introductions of contemporary scientific literature? To take one example, what would happen to contemporary views of brain function in health and disease if we removed that very large part of the Jacksonian tradition which is empirically questionable?

The trouble with theory is that sooner or later it parts company with reality, especially clinical reality, and must be replaced or modified. As Goldstein said, 'the patient can never be wrong'. Lashley's law of mass action and theories of cortical equipotentiality can be successful models for certain experimental paradigms, especially if the dependent variable is animal behaviour as a measure of, say, visual discrimination. But debates around these issues become sterile when translated into the clinical domain because the description of behaviour after human brain injury cannot give a full account of the experience of disability. Blindsight is not 'seeing' in its fullest sense. One can appreciate why clinical variables such as motivation and emotion and 'insight' (and Goldstein's 'abstract attitude') are not the central focus of the book. It is difficult enough to give a coherent account of recovery following the simplest brain lesions in the simplest of experimental systems without incorporating such complexities. But can they ever be avoided at the human level? A theoretical issue to which several contributors allude is the status of 'behavioural compensation' as opposed to neural mechanisms of recovery such as 'diaschisis' and 'vicariation'. There are no clear clinical criteria by which to identify behavioural compensation. And in any case, on what 'mythical and long-forgotten view' of brain function must this distinction be made?

The book reviews a variety of models of neural plasticity, functional adaptations and kindred subjects, and includes a provocative and timely review of neural implantation. There are one or two fairly heterodox offerings as well as coverage of the more familiar controversies. Editing is patchy and disappointing. Cross-referencing between chapters is incomplete. Contributors often fail to refer to each others' work, and the reader may be left to discover indirectly that two concepts or two bodies of literature, cited in different chapters, overlap or coincide. In contrast to Jackson's prose (typified by quotes in this book), lively and persuasive writing is supplied by several authors (but not by those who repeatedly write about the 'veracity' of phenomena, concepts, etc.). One wishes that the editors had combined forces to suggest a new conceptual framework within which contemporary issues could be explored experimentally. As it is, we have another multiauthor volume, incongruously overshadowed by the great theorists of previous generations.

Therapy also needs theories. *Rehabilitation of the Severely Brain-Injured Adult* makes a strong claim for basing rehabilitation on learning theory à la Pavlov and Skinner (who allegedly said 'the rat is always right'). As part of a series called *Therapy in Practice* the book is presumably addressed to members of the professional team, including doctors, who need to understand therapeutic principles. There are good short accounts of theories of functional recovery (including 'behavioural compensation') and of learning theory. It is interesting that declarative and procedural memory, as understood in the experimental and neuropsychological literature, get very short shrift. Surely the 'long-forgotten' subplot here is the relatively separate and autonomous development of the behavioural school of psychology to which the editors clearly belong. The result in this book is a distorted perspective contributing to errors, as on p. 72 where the 'amnesic syndrome' is described as a state in which 'the patient may be incapable of performing any complex series of actions'. The strongest parts of the book are those heavily dependent on clinical examples, giving one some idea of how therapy of severely brain-injured patients is conducted at the Kemsley Unit, Northampton, where all the contributors have connections. The use of formal systems of rewards and punishments is described. Discussion of ethical issues would have been welcome. The main professional rehabilitation activities are described in chapters of very variable quality. Literature on therapeutic systems is often cited without information on efficacy. A useful summary of motor learning theory occurs in a chapter on conductive education but there is no vital relationship between the two. One is left with the impression that the gap between theory and therapy will be reduced, but that there is still a long way to go.

CHRISTOPHER D. WARD

Carotid Artery Plaques. Pathogenesis—Development—Evaluation—Treatment. Edited by M. Hennerici, G. Sitzer and H.-D. Weger. 1987. Pp. 282. Basal: Karger. Price £36.40.

The problems debated at this German meeting at Güttesloh in January 1987 (Workshop on Carotid Artery Plaques, organized by the Bertelsmann Foundation and Department of Neurology, University of Düsseldorf) are important ones. Which factors determine the growth of arterial plaques? Why do they develop at particular sites, in particular in the carotid bulb? What makes a plaque rupture or ulcerate? Why do some become the site of mural thrombus formation with attendant clinical problems, whilst others remain stable and asymptomatic?

There is little in the papers on pathogenesis to illuminate the debate over whether endothelial injury, thrombus incorporation or lipid incrustation is the predominant factor in plaque growth, but there is much of interest in the discussion of physical factors. The flow characteristics at arterial bifurcations seem likely to be the deciding factor in the siting of plaques, and later in their chance of triggering thrombus attachment.

Epidemiological studies have revealed many so-called risk factors that predict the incidence of clinical events like heart attacks and stroke. Few studies reveal whether this reflects a connection between the risk factor and plaque growth, or the superadded thrombosis. Serial noninvasive imaging of arterial plaques by state of the art duplex scanning promises to reveal the role of hypertension, hyperlipidaemia, etc., on plaque growth and morphology. It is on these matters that this monograph is most successful. The clinical chapters include valuable reviews of different vascular occlusions (Caplan) and of endarterectomy and antithrombotic treatment (Wechsler, Bogousslavsky), but the data are available elsewhere.

Sadly one has yet again to decry the interval between debate and publication. Despite this I recommend interested parties to look at the papers on flow dividers, vortices, and velocity patterns which, though unfamiliar to most vascular clinicians, promise to illuminate much of the mystery of atherosclerosis.

M. J. G. HARRISON

The Lennox-Gastaut Syndrome. Edited by Ernst Niedermeyer and Rolf Degen. *Neurology and Neurobiology*, Volume 45, 1988. Pp. 483. New York: Alan Liss. Price $88.00.

This is a multiauthor book that attempts to cover in a comprehensive fashion this complex subject. The Lennox-Gastaut syndrome represents one of the most troublesome and malignant of the childhood epilepsies. People who have suffered from this syndrome not infrequently will ultimately become adults with epilepsy but, as an adult neurologist, one can only be relieved that by the time that this occurs the epilepsy has usually become much less severe and less varied in its seizure expression, although the patients are usually moderately to profoundly retarded. The syndrome continues to raise many crucial questions about the nature of epilepsy itself. Is this syndrome simply a part of a continuum in continuity with the Ohtahara syndrome and West's syndrome? Can the diagnosis be accepted in those with seizure onset in late childhood and adolescence? Is the cognitive decline and retardation found in these children a result of the frequent seizures themselves or an expression of a progressive cerebral pathology independent of seizures? Is any therapy truly effective in these children, and if so is early treatment essential to obtain a satisfactory outcome?

The book is the product of the proceedings of a symposium held in West Germany in September, 1987. The chapters have been produced from camera-ready manuscripts, presumably to speed the publication. In the days of desk top publishing one questions how often such an approach should be necessary. Certainly the quality of type face and illustrations is very variable and one wonders whether a greater editorial input would not have been helpful, particularly as it is very clear that most of the authors are not writing in their first language. Having said this, the authors have produced a number of very high standard chapters which successfully cover historical, clinical, electroencephalographic and neuropathological aspects of the condition. Inevitably, there is at times considerable overlap and repetition between some chapters. The consideration of therapeutic approaches to the condition is particularly helpful, ranging from alternative approaches including dietary measures through to callosotomy. An unusual feature is the inclusion of a number of free communications as supplementary chapters.

There is no doubt that this book should for some time be a standard reference book for anyone wishing to explore the ramifications of this childhood epileptic syndrome. It is likely, however, to remain a book for those with a specialist interest rather than for the general neurologist.

David Chadwick

Therapeutic Claims in Multiple Sclerosis. Second edition. William A. Sibley and the Therapeutic Claims Committee of the International Federation Multiple Sclerosis Societies. 1988. Pp. 198. Basingstoke: Macmillan. Price £7.95 (paperback).

This paperback is a welcome replacement for its predecessor which had hard covers, ring binders and loose pages. It fulfils its claim to be an ideal guide for patients wanting information about treatment but it lacks references and will not be much use to neurologists except to pass on to their patients. Over 100 different treatments are considered. Each evaluation is concluded by a stereotyped italicized statement which one can almost hear enunciated in computerized tones by the word processor: 'In the opinion of the committee there appears to be no generally accepted scientific basis for use of this therapy.' Particularly intriguing was the straw poll of the ten members of the committee concerning their preferences for treating relapses or slow progression of multiple sclerosis. There were almost as many policies as committee members. It was disappointing to see physiotherapy and occupational therapy relegated to half a page since their help is probably more beneficial to patients than the whole neurological pharmacopoeia.

R. A. C. Hughes

Cerebral Hemisphere Function in Depression. Edited by Marcel Kinsbourne. 1988. Pp. 190. Cambridge University Press. Price £18.50.

Psychophrenology is undergoing a revival. Attempts to link psychopathology to specific brain structures have been made with renewed enthusiasm since the advent of new imaging techniques. These efforts, often simplistic, are based on the model of neurological disease where focal neuropathological changes are often present. This inappropriate analogy has led to the narrow search for the anatomical counterparts of schizophrenic and affective symptoms. It is therefore refreshing to find a book where more space is devoted to the complex conceptual issues than to the rarely satisfying studies.

This book is part of the *Progress in Psychiatry* series and its contents are based on the theme of a symposium organized by the American Psychiatric Association. My natural inclination is to be wary of such books which often sacrifice quality for the dubious benefits of prompt publication, but this is an exception. The book is brief, readable and with contributions of quality. Some of the chapters like the one by Starkstein and Robinson on emotional response after stroke would be familiar to many. Others dealing with the effects of right hemisphere damage and with intra-hemispheric balance in emotional disorder are less familiar and worth reading. The book also includes a brief review of recent PET and EEG studies and a good chapter by Kinsbourne on the interaction of right and left hemispheres in emotion. A final overview by Galin draws together the various contributions and whilst no definite answers are forthcoming, oversimplifications are carefully avoided. Perhaps the subject-matter makes the book interesting to a restricted public, but those curious about brain-behaviour interactions will also find it useful.

MARIA RON

Psychopharmacology of the Ageing Nervous System. *Handbook of Psychopharmacology*, Volume 20. Edited by Leslie L. Iversen, Susan D. Iversen and Solomon Snyder. 1988. Pp. 482. New York: Plenum. Price $75.00.

As is appropriate for the series, the main theme of the book is the pharmacology of dementia especially in relation to the presynaptic cholinergic defect in Alzheimer's disease. Different contributors review the topic from their own perspective and inevitably there is some textual overlap. However, all are well-written critical accounts with extensive citations to the literature mostly to the end of 1986. The book is distinctive in that authors identify problems and speculate about the mechanisms of pharmacological responses.

The first 5 chapters cover the neuropathology and neurochemistry of dementia including those associated with Parkinson's disease, alcoholism and subcortical dementias. The reviews are wide-ranging and scholarly. Next there is a review of evidence for genetic vulnerability as suggested by the familial aggregation of Alzheimer's disease. Why, asks Breitner in Chapter 6, does the putative gene require 80 years for its expression? The current controversy on the amyloid precursor gene and its products or the recent linkage studies on familial Alzheimer's disease are not covered.

There follows a long (nearly 90 pages with 360 references) review of the value of animal experiments in relation to the cholinergic hypothesis of memory. The authors wisely conclude that it is misleading to overemphasize agreement between animal studies or to overstress the global significance of the cholinergic deficit in dementia. In their chapter on behavioural models of ageing in nonhuman primates, Dean and Bartus argue that there are reliable models of age-related memory impairments which are of potential value in the treatment of cognitive problems in Alzheimer's disease. This theme is elaborated in the remainder of the book where the use of cholinergic and other drugs is reviewed. The book can be recommended as a thoughtful reference book, particularly for those clinicians and neuroscientists searching for useful therapeutic agents for the treatment of Alzheimer's and related dementias.

A. N. DAVISON

A Colour Atlas of Multiple Sclerosis and Other Myelin Disorders. By Colin Adams. 1989. Pp. 231. London: Wolfe. Price £55.00.

With its 10 chapters this colour atlas deals not only with the various aspects of multiple sclerosis, but also with other diseases of the myelin sheath that bear any epidemiological, pathogenetic or morphological resemblance to this debilitating illness.

After a preliminary section on the structure and components of the myelin, the process of myelination and the mechanisms of demyelination, and remyelination, subsequent chapters deal with acquired and genetically induced demyelinating processes in man and animals (Chapters 2 and 3), and experimentally produced myelin breakdown (Chapter 4). The part of the book devoted to multiple sclerosis begins with an overview on the aetiology and epidemiology of the disease (Chapter 5) and is followed by a detailed description of its macroscopic (Chapter 6), histological and cytological (Chapter 7) appearances. The involvement of the vessels and their pathogenetic role in the demyelinating process is extensively treated in Chapter 8, while a rather short but comprehensive Chapter 9 is devoted to the serological and cellular immunology of multiple sclerosis. The last chapter describes the complications and causes of death in patients with this disease, a reminder to pathologists of the many damages a disease confined to central nervous system can produce.

Each chapter comprises a text of variable length and a vast number of colour illustrations. The occasional mislabelling of pictures in the text and the poor quality of only an occasional one of them should not prevent praising the overall excellent quality of the illustrations. Yet, perhaps surprisingly for a book that is presented as an atlas, it is the text that most attracted my interest. It is rather concise, but comprehensive; it describes facts, gives well thought opinions, quotes other workers' experience and is accompanied by a generous bibliography. The account of all the aspects of multiple sclerosis and other demyelinating diseases gives the reader a thorough overview of the many problems related to this disease. Statements such as that on page 87 considering some human diseases as 'human counterparts of experimental categories' are perhaps overestimating the similarities and should be regarded with scientific scepticism; the same could be said of the comparison between ring haemorrhages in acute haemorrhagic leucoencephalopathy and in multiple sclerosis. Such cases are, however, few in number and do not diminish the overall objectivity of the description.

In conclusion, this is a delightful, extremely interesting book which I do not hesitate to commend and suggest as a useful aid in everyday work in the field of demyelinating diseases. The price should not be a deterrent.

FRANCESCO SCARAVILLI

Novel Infectious Agents and The Nervous System. Ciba Foundation Symposium 135. 1988. Pp. 277. Chichester: John Wiley. Price £30.50.

This volume contains 15 papers presented at a symposium on unconventional virus diseases held in London in 1987. The emphasis is on the remarkable developments in the understanding of the scrapie agent and the properties of the component prion protein. Other chapters discuss the neuropathology of this group of conditions, the relationship between amyloid (A4) protein in Alzheimer's disease and prion protein, and a timely article focusing on iatrogenic Creuzfeldt-Jakob disease. All the contributions contain valuable and often new information, and each is followed by a stimulating and at times revealing discussion of the implications of the data presented. One disadvantage of this type of format is that important findings may be mentioned in passing without further comment. In the chapter by Manuelidis *et al.*, for example, the successful transmission of Alpers' disease is reported, although the implications of the transmission of this recessively inherited spongiform degeneration of childhood are not further examined. Nonetheless this book provides an insight into the continuing controversy over the fundamental nature of the agent or agents in this group of conditions.

The contributions from Prusiner *et al.*, Oesch *et al.* and Carlson *et al.* support the prion theory of infectivity, which proposes a self-replicating membrane protein devoid of nucleic acid. It has been established that there are two isoforms of prion protein. PrP^{C} is a component of normal cells while PrP^{Sc} segregates with infectivity and in contrast to PrP^{C} is resistant to protein kinase K, presumptively because of posttranslational modification. PrP^{Sc} can be induced in vitro to aggregate into structures similar in structure to the prion rods which accumulate in the extracellular space in scrapie and Creutzfeldt-Jakob disease to form amyloid plaques. Hope *et al.* provide convincing evidence to suggest that the Sinc gene, which controls the incubation period in murine models, and the gene for PrP are closely linked and that PrP may even be the protein product of the Sinc gene.

Other contributors contest this interpretation of the evidence and propose that the agent is a virino, containing nucleic acid, which utilizes the host genome to provide a coat of PrP, thereby rendering the agent nonimmunogenic and difficult to isolate. This theory more readily explains the strain variation in scrapie described by Dickenson *et al.*, the shortening of incubation period in serial experimental passage of these agents, and the kinetics of agent replication described by Kimberlin and Walker. Using long incubation models, this article confirms early replication in the reticulo-endothelial system with spread of the agent to the spinal cord and thence to the brain. Neural transport of the agent is suggested by the development of infectivity in the superior colliculus after introduction of infection in the contralateral eye and it is proposed that the prolonged incubation in the brain (more than 50% of the total incubation period) relates to delay in infection of 'clinical target areas' and limitation of replication in the CNS.

A third proposition that the agent is a conventional virus, perhaps of the retrovirus group, is argued by Manuelidis *et al.*, who present data on tissue culture of Creutzfeldt-Jakob disease infected neurons which secrete a transforming growth factor and become oncogenic, properties reminiscent of some conventional viruses. Further support for a viral aetiology is provided by the loss of infectivity in purified prion protein and the low infectivity of organs known to be rich in this protein. Caughey *et al.* demonstrate that the protein expressed by cloned PrP cDNA derived from scrapie-infected mice is noninfectious, although posttranslational modification of this protein is probably essential for infection.

Another topic, discussed by Diringer *et al.* and other contributors, is the amyloid protein which aggregates to form the characteristic prion rods or scrapie-associated fibrils. Wisniewski *et al.* demonstrate that the amyloid in scrapie is distinct from that in Alzheimer's disease or Down's syndrome, although the development of amyloid plaques in unconventional virus diseases is in general related to extended duration of disease. An exception are the cases of Creutzfeldt-Jakob disease in growth hormone recipients in which a prolonged atypical clinical course is not associated with significant accumulation of amyloid protein. Brown relates the unusual clinical features in these cases to the inoculum dose and route of infection and it is of interest that only 2 of the patients were diagnosed in life.

This is an excellent book and is essential reading for those with an interest in this field. No final conclusion can be drawn about the nature of the agent in unconventional virus diseases or indeed whether the agents of scrapie and Creutzfeldt-Jakob disease are identical. Case-to-case or species-to-species transmission occurs in scrapie, Kuru, transmissible mink encephalopathy and almost certainly in bovine spongiform encephalopathy. This volume confirms that strain variation of the agents, genetically controlled host factors, and differing routes and dosage of infection all have profound effects on the incubation period or whether disease develops at all. In this context one wonders whether a novel biological mechanism of infection involving a genetically integrated agent is necessary to explain the epidemiology of these conditions and in particular of Creutzfeldt-Jakob disease.

R. G. WILL

Evoked Potentials III (The Third International Evoked Potentials Symposium, Berlin, 1986). Edited by Colin Barber and Thomas Blum, 1988. Pp. 478. Boston, MA and Sevenoaks, Kent: Butterworths. Price £98.00.

Since the first of these symposia, evoked potential techniques have been pressed into an ever-increasing variety of clinical and nonclinical applications. The scope of the present volume, comprising 68 reviews and research papers selected from those presented in Berlin, is therefore very wide. Its main appeal is likely to be to electrophysiologists with a general interest in evoked potentials as a means of accessing human sensory processes in their normal and pathological state, who may find it difficult to keep abreast of current developments by casual appraisal of the journals.

The first section of 114 pages is devoted to 'Background and Perspective' and consists of 8 review articles, mostly of a high quality. A significant recent advance in the understanding of so-called 'far-field' potentials (an appropriate definition of which would be those which fail to diminish in amplitude according to the square of their distance from the generator) was prompted by Kimura's examination (here reviewed) of the electric fields associated with antidromic propagation of a sensory nerve action potential. The complementary insights which have been achieved using a potential field modelling approach are illustrated in a research paper by Stegeman. Other notable reviews include those by McCallum on the relationship between long-latency evoked potentials and cognitive function, Allison on the effects of maturation and ageing, and Kaufman on recent developments in recording the evoked magnetic fields of the brain. The article by Lehmann on the automatic derivation and analysis of evoked potential 'maps' is extremely valuable from a technical point of view, as is the research paper by Perrin on scalp current density mapping, but there is still some doubt as to whether this much-vaunted (by the manufacturers) and occasionally abused facility is likely to open up many new avenues of research.

Most of the research papers are conventionally divided into the auditory, visual and somatosensory modalities, of which it would seem to be the somatosensory which has been the most fertile in recent years. From a number of worthwhile studies one would single out that by Katifi on the use of dermatomal stimulation to localize lumbar root lesions, similar techniques being employed by Toleikis to investigate traumatic spinal cord and root lesions. Rossini provides some useful observations on the relationship between somatosensory evoked electric and magnetic fields, which may help to resolve some longstanding disagreements in the literature. The evaluation by Schramm of the relative merits of cortical and spinal SEPs in monitoring the status of the spinal cord during surgery is also timely, in view of the growing number of surgeons who see such procedures as a desirable addition to the technology of the operating theatre.

In the section on visual evoked potentials, several authors address more or less abstruse aspects of the stimulus-response relationship, whereas others are concerned with more practical matters such as developing an effective technique for monitoring the visual pathway during surgery (Harding) or exploring the diagnostic possibilities of the pattern-evoked electroretinogram (Holder, Celesia). With far fewer degrees of freedom to appeal to sensory physiologists, the auditory evoked potentials lend themselves to straightforward applications such as monitoring the status of the brainstem during cerebellopontine angle surgery (Hochstetter) or the effects of anticonvulsant drugs (Medaglini). A section on 'Multimodal Applications of Evoked Potentials' is also largely practical in content, ranging from a preliminary examination of the incidence of abnormalities in AIDS (Comi) to the effects of hypothermia during cardiopulmonary bypass surgery (Rimpel).

The possibility that long-latency event-related potentials might be used as an index of pathological as well as normal cognitive function has recently attracted considerable attention. Various authors attempt to characterize the defects associated with 'cortical' and 'subcortical' dementias (Goodin), solvent exposure, alcohol abuse and depression (El Massioui), migrainous and nonmigrainous headache (Timsit) and schizophrenia (Maurer), without providing this reader with much sense of an imminent breakthrough. On the other hand, the maturational effects described (without statistical encumbrance) by Taylor are both convincing and intriguing. Most of the remaining papers in this section cover aspects of the normal relationship between evoked potentials and cognitive function, with a wide variation in theoretical and methodological sophistication.

A short concluding section departs from the usual view of evoked potentials as representing purely sensory phenomena, and consists of 5 papers describing or utilizing motor responses to invasive and noninvasive cortical stimulation. Respective articles by Rossini and Hess describe, with considerable authority, the principal findings using transcranial electrical and magnetic stimulation of the human brain, but these may already be somewhat out of date.

S. J. Jones

Physiological Aspects of Clinical Neuro-ophthalmology. Edited by C. Kennard and Clifford F. Rose. 1988. Pp. 482. London: Chapman and Hall. Price £35.00.

The editors asked the participants of a meeting held in 1986 at the Medical Society of London sponsored by the Mansell Bequest to prepare a chapter in their area of expertise. The multiauthored book is a compilation of articles and reviews which covers in 28 chapters a wide range of topics such as optic disc oedema, visual agnosia, eye movement generation and regulation of pupillary size. The close juxtaposition of clinically and research orientated approaches gives a mixture of contributions, the quality of which is quite diverse. While some chapters are an admirable guide to recent work, others are not quite as up-to-date as one would have hoped and summarize data which are already well known or for which the clinical relevance is not obvious. Chapters 1, 14 and 17 on the testing of visual acuity and fields, cortical control of eye movements, and the vestibulo-ocular reflex, respectively, are scholarly and well balanced, stressing conceptual problems. Chapters 16 and 19, on the other hand, dealing with the role of the cerebellum in eye movement regulation, are not well coordinated and do not discuss clinical and conceptual problems adequately, and Chapter 10 on visual agnosia is too detailed and heavy-going.

Thus while some chapters are quite excellent, the parts do not add up to a coherent whole, as with most multiauthor books. Nevertheless, the book provides a useful collection of contributions for those active in the field. It may not be very helpful in clinical practice but it increases the understanding of anatomical and physiological aspects in some rapidly advancing areas of neuro-ophthalmology.

W. Waespe

Neurophysiology of the Vestibular System. Edited by L. Pirodda and O. Pompeiano. *Advances in Oto-Rhino-Laryngology*, Volume 41. 1988. Pp. 243. Basel: Karger. Price DM 205.00.

I was pleased to be asked to review a book called *The Neurophysiology of the Vestibular System*, having felt for some time that a book on this topic was needed as Wilson and Melville Jones' admirable volume (V. J. Wilson and G. Melvill Jones, *Mammalian Vestibular Physiology* (1979, New York: Plenum)) is now 10 years old. So frankly I was rather disappointed when I realized that *The Neurophysiology of the Vestibular System* was merely another collection of conference proceedings. Together with its companion volume *Clinical Testing of the Vestibular System*, this book is the proceedings of the Bárány Society meeting that took place in Bologna in the summer of 1987. The Bárány Society is an excellent society, truly representing those responsible for the main thrust of vestibular research and having the additional noble aim of combining clinical and pure science approaches. As such, its meetings are attended by a cross-section of the most important vestibular researchers and clinicians, many of them represented in this volume. The reputation of the Bárány Society is reflected in the quality of the papers and, refereed or not, they do represent some of the most exciting areas.

There were some outstanding papers presented at the meeting, but essentially only their abstracts are presented here: authors were limited to 4 pages including figures and references. The papers in full form will thus appear elsewhere in refereed journals, away from the strict restrictions of space that conference proceedings demand. The picture on the front cover illustrates the limitations. It is from Muriel Ross's work applying the extremely exciting and popular ideas of networking to the otolith end-organ. But her frontier-forging paper has less than 3 pages of text and can only hint at her subject. So one may deduce that something exciting is going on but there is not enough information to know exactly what and still less to evaluate it for oneself.

The editors claim to have selected from manuscripts submitted at the meeting. There were, in fact, 143 papers presented at the meeting and the two volumes contain the abstracts of 105 of them. It is very unclear by what criterion the papers could have been selected: there is certainly no evidence of theme, or even an attempt to organize the papers into sections. There is no commentary or introduction that might make the papers more accessible to a nonspecialized audience. This is partly in the interest, I presume, of speedy publication; in this the editors are to be congratulated, the time-to-publication seems quite reasonable.

The Bárány Society also hosted two satellites within its Bologna meeting. These were on the representation of three-dimensional space in the vestibular system and the vestibulospinal control of posture and movement. These two topics are of particular interest at the moment but, not surprisingly since they will be published in separate volumes, are hardly represented here. Their existence undermines the editors' bold claim to 'offer the latest and most significant findings in current vestibular research'.

There is an important place for conference proceedings—there is a need for people, perhaps those on the edge of the field, perhaps graduate students, to have speedy access to collections of papers that represent the important areas. But such people can be much assisted by conscientious editing. They need papers to be selected as being the best or most representative of an area. They need background information, and they can benefit from a straight confession that some important areas are *not* covered in a volume. They certainly need more background information than can be put in a 3-4 page abstract.

Advances in Oto-Rhino-Laryngology is an ideal place to publish this particular conference. But such volumes should not be confused with, or made easily confusable with, Real Books. *Bárány Society Meeting 1987* should be the main title and *Neurophysiology of the Vestibular System* a subheading. At the moment the presentation seems misleading, apparently attempting to seduce those who are looking out for an update of Melvill Jones and Wilson. So, in summary, the book is an adequate collection of illustrated conference abstracts. Meanwhile, I look forward to reviewing a book on *The Neurophysiology of the Vestibular System*.

LAURENCE HARRIS

ANNOUNCEMENTS

Fourteenth World Congress of Neurology

This will be held in New Delhi on October 22–27, 1989. Further information may be obtained from the Secretariat to the XIVth World Congress of Neurology, Department of Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India.

International Merritt-Putnam Symposium

A symposium on 'Epilepsy: Delivery of Quality Care with Limited Resources' will be held on October 21–22, 1989, in conjunction with the 18th International Epilepsy Congress and the XIVth World Congress of Neurology in New Delhi, India. Further information may be obtained from Ruben Gutierrez, Intramed Communications, 1180 Avenue of the Americas, New York, NY 10036, USA.

Association for Research in Nervous and Mental Diseases

A meeting on 'Genes, Brain and Behavior' will be held on December 1–2, 1989, at the Roosevelt Hotel, New York City. It will be cosponsored by the New York Academy of Medicine. For further information, contact Dr Ivan Bodis-Wollner, Secretary-Treasurer, ARNMD, Box 1052, Mount Sinai Hospital, 1 Gustave Levy Place, New York, NY 10029, USA.

European Neurological Society

The second ENS congress will be held in Brighton, England, on June 30–July 4, 1990. This will include teaching courses, symposia, and platform and poster presentations. The deadline for the submission of abstracts is January 15, 1990. For further details, contact ENS 1990, Concorde Services Ltd., 10 Wendell Road, London W12 9RT, UK.

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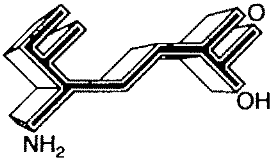

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EFFECT OF ION CHANNEL BLOCKERS ON IMMUNE RESPONSE AND COURSE OF EXPERIMENTAL ALLERGIC NEURITIS

by EILHARD MIX,[1*] TOMAS OLSSON,[1] GÖRAN SOLDERS[1,2] *and* HANS LINK[1]

(From the Departments of [1]Neurology and [2]Clinical Neurophysiology, Karolinska Institutet, Huddinge University Hospital, Stockholm, Sweden)

SUMMARY

The influence of the K^+ channel blocker quinidine and the Ca^{++} channel blocker verapamil on in vivo and in vitro immune responses was tested in experimental allergic neuritis (EAN) of Lewis rats. Daily intraperitoneal injections of 4 mg quinidine produced a significant reduction of neurological deficits in EAN rats, whereas verapamil had no effect. In contrast, both drugs inhibited the in vitro proliferative response of regional lymph node cells to specific antigens of bovine peripheral myelin and purified protein derivative of tuberculin in a similar dose-dependent manner. Quinidine-treated EAN rats revealed considerably less inflammatory infiltration in target tissue than untreated EAN rats, shown immunohistochemically. Single injections of ion channel blockers into EAN rats did not improve nerve cell functions as measured by electrophysiological recordings of sciatic nerve. It is concluded that the dominant effect of quinidine in vivo is attributed to a reduction of the demyelinating autoimmune process. Hence ion channel blocking drugs can exert immunomodulatory effects, which may have implications for their clinical application.

INTRODUCTION

The mitogenic response of lymphocytes can be inhibited in vitro by K^+ channel blockers (DeCoursey *et al.*, 1984) and Ca^{++} channel blockers (Nel *et al.*, 1986). The mechanism may relate to an interference with transmembrane signalling and subsequent steps in cell activation, especially those regulated by the level of intracellular Ca^{++} concentration ($Ca^{++}{}_I$) (Tsien *et al.*, 1982; Alcover *et al.*, 1986; Gelfand *et al.*, 1987; Kuno and Gardner, 1987; Gupta *et al.*, 1988; MacDougall *et al.*, 1988). Hitherto most studies were performed on nonspecific lymphocyte stimulation in vitro. There are reports that similar mechanisms may also apply to antigen-specific immune reactions (Birx *et al.*, 1984; O'Flynn *et al.*, 1985; Nisbet-Brown *et al.*, 1987). It should therefore be of interest to study the effects of ion channel blockers on specific immune responses in vivo, especially in immune-mediated diseases.

Experimental allergic neuritis (EAN) (Waksman and Adams, 1956) induced with components of peripheral nerve and Freund's complete adjuvant is regarded as a useful

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Correspondence to: Dr Tomas Olsson, Department of Neurology, Karolinska Institutet, Huddinge University Hospital, S-141 86 Huddinge, Sweden.

[*] Guest scientist from the Clinic for Psychiatry and Neurology, Wilhelm-Pieck University, Rostock, GDR.

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model. It reveals a predictable acute monophasic clinical course with paresis of the tail and the hindlimbs. Lymphocyte transfer experiments have demonstrated the crucial role for T cells in disease induction (Åström and Waksman, 1962; Arnason and Chelmicka-Szorc, 1972; Linington *et al.*, 1984). In our laboratory studies on target immune responses (Olsson *et al.*, 1983, 1984; Strigård *et al.*, 1987) and treatment with anti-T cell antibodies (Holmdahl *et al.*, 1985; Strigård *et al.*, 1988) clearly showed T cell dependency of the effector phase of the disease. We now used this model to study the effect of the K^+ channel blocker quinidine and the Ca^{++} channel blocker verapamil on specific immune responses in vivo and in vitro.

In vivo treatment with quinidine reduced significantly the clinical manifestations of the disease whereas verapamil had no effect, although both drugs suppressed the in vitro proliferative response of regional lymph node cells (LNC) to neuritogenic bovine peripheral myelin (BPM) and purified protein derivative of tuberculin (PPD) in a similar dose-dependent manner.

Quinidine-treated and control EAN rats were examined for inflammatory infiltration into the target tissue immunohistochemically and for nerve cell function by electrophysiological recordings of sciatic nerve. K^+ channel blockers improve nerve conductivity in certain types of demyelination (Sherratt *et al.*, 1980; Targ and Kocsis, 1985). We therefore additionally assessed nerve cell function under the short-term influence of ion channel blockers.

MATERIAL AND METHODS

Induction of EAN and assessment of clinical signs

Lewis rats originally obtained from Antimex (Stockholm, Sweden) were immunized by injection into each hindfoot pad of 0.1 ml inoculum containing 1 mg Mycobacterium tuberculosis (ST 37 RA, Difco, Detroit, USA), 0.05 ml saline, 0.05 ml Freund's incomplete adjuvant (Difco, Detroit, USA), and 2 mg BPM prepared as described elsewhere (Kadlubowski *et al.*, 1980).

Body weight and clinical symptoms were assessed every second day. Neurological deficits were graded as follows: 0 = no illness, 1 = limp tail, 2 = moderate paraparesis, 3 = severe paraparesis, 4 = tetraparesis. Assessments were made by an independent person unaware of treatment regimens. Changes in body weight were calculated according to the equation: body weight = $((a-b)/b) \times 100$, where a = body weight at assessment, and b = body weight immediately before immunization.

In vivo treatment with ion channel blockers

Simultaneously with the induction of EAN, rats received intraperitoneal injections of 4 mg quinidine (Kinidin, ACO, Stockholm, Sweden) dissolved in 1 ml sterile saline. The injections were repeated daily thereafter. Control EAN rats received daily injections of 1 ml saline only. Experiments were done in 4 series involving 5–7 animals each.

In one series of experiments a group of 6 EAN rats was treated with 1 mg verapamil (Isoptin, Knoch, Ludwigshafen, FRG) in the same manner as the quinidine treated group. Since this dosage did not effect EAN we started another series of experiments with 2 mg verapamil per injection, but this dosage was not tolerated since the animals exhibited evidence of partial shock.

The Mann-Whitney rank test was used for statistical analysis of differences in body weight (*see* fig. 2) and accumulated disease score (sum of pareses for each rat) between treated and untreated EAN rats.

Lymphocyte proliferation assay

Suspensions of popliteal and inguinal LNC taken between days 9 and 16 after induction of EAN were prepared in sterile phosphate-buffered saline, pH 7.4 (Flow Laboratories, Herts, UK). Cells were washed twice and resuspended in Dulbecco's modified Eagle's medium (DME, Flow Laboratories, Herts, UK) supplemented with nonessential amino acids (MEM, Flow Laboratories, Herts, UK), 2×10^{-3} M glutamine (Gibco, Paisley, UK), 5×10^{-5} M mercaptoethanol (Merck, Darmstadt, FRG), antibiotics (PSN antibiotic mixture, Gibco, Paisley, UK), and 1% fresh normal rat serum. The cell suspension was adjusted to $2-5 \times 10^{6}$ viable cells/ml DME; 200 μl aliquots of cell suspension were placed in 250 μl wells of 96-well microtitre plates (Nunc, Copenhagen, Denmark).

For lymphocyte stimulation, 10 μl aliquots of antigens, PPD (Statens Seruminstitut, Copenhagen, Denmark) and BPM were added to obtain final concentrations of 50 μg/ml and 20 μg/ml, respectively. In blocking experiments, 10 μl aliquots of serial dilutions of the ion channel blockers quinidine and verapamil (both from Sigma Chemicals, St. Louis, USA) were added to obtain the final concentration indicated in fig. 3. All stock solutions of antigen and drugs were prepared freshly in sterile saline and diluted in DME immediately before use. In control cultures the respective volumes were replaced by DME alone. In some experiments the phorbol ester 12-O-tetradecanocyl-phorbol-134-acetate (TPA) was applied concomitantly with the ion channel blockers.

Cells were incubated for 3 days at 37° C in humidified 5% CO_2 . At 16 h before cell harvest, 10 μl aliquots containing 1 μCi of ^{3}H-methyl-thymidine (Amersham, Little Chalfont, UK) in saline were added to each microtitre well. Cells were harvested onto glass fibre filter strips (Skaltron AS, Lierbyen, Norway) with a multiple-channel semiautomated harvesting device (Titertek, Saktron AS, Lierbyen, Norway) followed by repeated washings in distilled water.

The radioactivity incorporated into cellular DNA was counted in a beta-scintillation counter (mark II, Searle, Analytic, Des Plaines, USA). The mean counts/min (cpm,) and SDS of ^{3}H-thymidine incorporations were calculated from triplicate wells. Results of blocking experiments are expressed as suppression of lymphocyte proliferation percentage (*see* fig. 2).

Immunohistochemistry

On day 16 after induction of EAN, sciatic nerves were dissected, snap-frozen in liquid nitrogen, and kept at −70° C until cryosection; 8 μm section were stained for phenotyping of cells by applying appropriate dilutions of the following primary monoclonal antibodies (MAB): Ox19 = antirat CD5, pan-T-cells (Dallman *et al.*, 1984); Ox8 = antirat CD8, T 'cytotoxic/suppressor' cells (Brideau *et al.*, 1980); W3/25 = antirat CD4, T 'helper' cells and macrophages (Williams *et al.*, 1977; Barclay, 1981); Ox39 = antirat interleukin 2 (IL2) receptor (Sedgwick *et al.*, 1987); and Ox6 = antirat class II transplantation antigens (McMaster and Williams, 1979). All MAB except Ox39 were gifts from Dr Lars Klareskog (Department of Medical and Physiological Chemistry, Uppsala University, Uppsala, Sweden). They were purified from culture supernatants (Holmdahl *et al.*, 1985) of hybridomas originally obtained from Dr Alan Williams (Oxford, UK). Ox39 was purchased from Seralab (Crawley Down, UK). The avidin-biotin peroxidase method was used for final staining applying the ABC Vectastain Kit (Vector Lab., Burlingame, USA). For control of staining specificity, the primary MAB was omitted and no nonspecific staining was seen.

Neurophysiological recordings

Two groups of 6 EAN rats were investigated. One was treated with quinidine as described, and one injected with saline for control. Recordings were done before (day 0) and 14 days after the induction of EAN. In a second experiment the control EAN rats received single injections of 4 mg quinidine (n = 2), 1 mg verapamil (n = 2) and 1 mg 4-aminopyridine (4AP) (n = 2), respectively. Recordings were done at day 14 immediately before drug injection and 10 min and 30 min later.

The animals were anaesthetized by repeated intramuscular injections of 50 μl Hypnorm (fluanisone 10 mg/ml+fentanyl 0.2 mg/ml, Janssen Pharmaceutics, Beerse, Belgium) diluted in saline.

Nerve stimulation and recording of muscle responses were performed using conventional

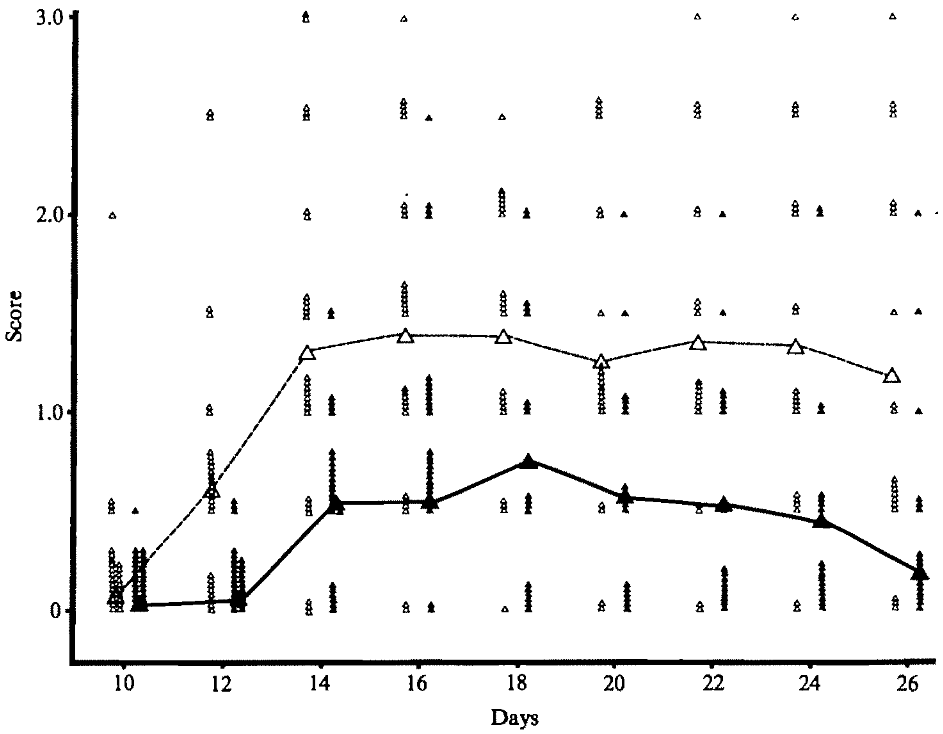

FIG. 1. Effect of quinidine treatment on the clinical course of EAN. Rats received daily intraperitoneal injections of 4 mg quinidine in 1 ml saline starting simultaneously with the induction of EAN. The EAN control animals were injected with an equivalent volume of saline alone. The severity of symptoms was graded as described in Materials and Methods. Filled triangles represent values of quinidine-treated animals and open triangles represent values of control animals. Mean values are indicated by enlarged symbols.

neurophysiological equipment (Medelec MS6, Old Valley, UK). Sciatic nerve stimulation was delivered through hypodermic needles inserted at the sciatic notch and at the knee with the anode inserted in the flank and the ground electrode subcutaneously at the ankle (Kaeser and Lambert, 1962; Saida *et al.*, 1980). Recordings were made with a concentric bipolar electrode inserted in the first interosseous space. A 0.1 ms stimulus pulse was delivered and increased until a supramaximal muscle response could be recorded.

The latency, duration and peak-to-peak amplitude of the muscle response were measured after proximal and distal nerve stimulation and the amplitude ratio (proximal/distal stimulation) was calculated.

The neurophysiological data are given as mean ± SD. Intraindividual differences between day 0 and day 14 after EAN induction were compared using the t test for paired observations. Quinidine treated animals were compared with untreated animals at day 14 using the t test with compensation for significant difference in variance between the two groups compared (Snedecor and Cochran, 1980). This test was used since the variances differed significantly between the two groups when F-tested (Snedecor and Cochran, 1980).

RESULTS

Clinical course

Surveys of clinical scores and body weights are presented in figs 1 and 2, respectively. Later onset, shorter duration and milder clinical signs characterized the quinidine treated

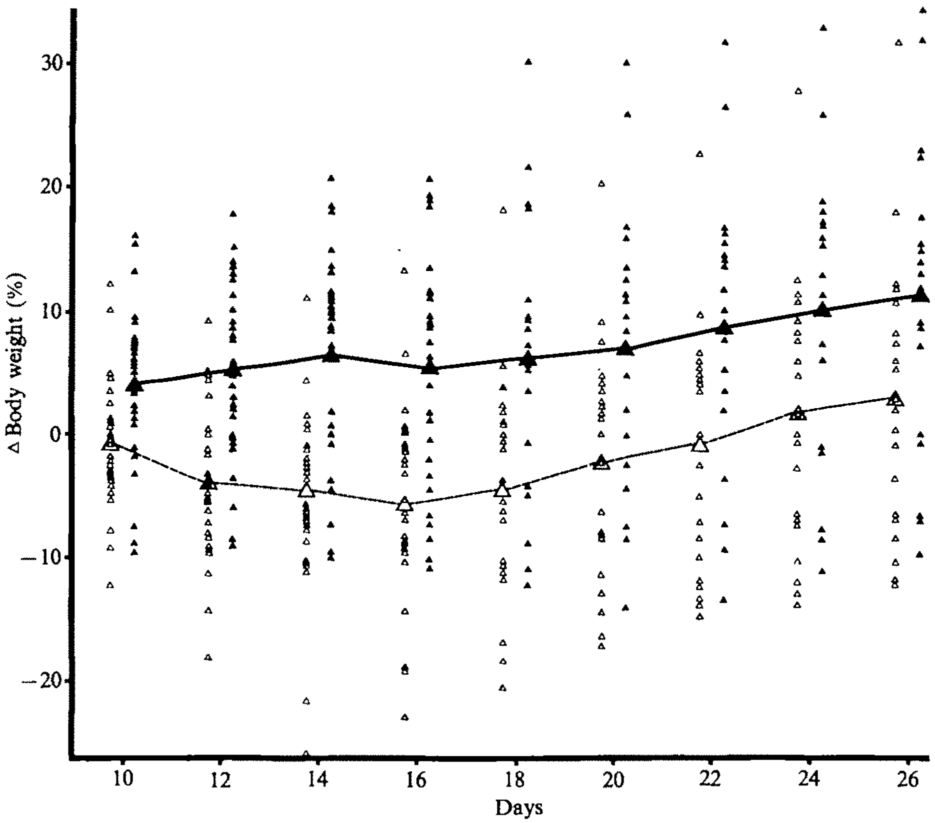

FIG. 2. Effect of quinidine treatment on body weight of EAN rats. Rats received daily intraperitoneal injections of 4 mg quinidine in 1 ml saline simultaneously with the induction of EAN. The EAN control animals were injected with an equivalent volume of saline alone. The relative changes of body weights were calculated as described in Materials and Methods. Filled triangles represent values of quinidine-treated animals and open triangles represent values of control animals. Mean values are indicated by enlarged symbols.

EAN rats as compared with the saline injected EAN control rats (fig. 1). The experiments were performed in four different sessions in order to test the reproducibility of the registered effects. In all the individual series the same influence of quinidine was observed. However, the difference in the clinical signs in EAN controls were considerably greater between the different sessions than between rats within one session, probably due to variable content of neuritogenic components in the BPM batches. In spite of this, when comparing all animals simultaneously, a statistically significant difference between treated and untreated animals for accumulated scores was observed ($P < 0.01$). Due to different body weights of animals between the different sessions at the time of EAN induction, the variation in changes of body weight during the course of the disease was rather large when considering the results of all animals (fig. 2). Nevertheless, the difference between treated and untreated animals was statistically significant according to the rank test of accumulated changes of body weight ($P < 0.01$). Verapamil treated EAN rats

TABLE 1. ESTIMATION OF T CELLS AND CLASS II TRANSPLANTATION ANTIGEN EXPRESSING CELLS IN UNTREATED AND QUINIDINE TREATED EAN RATS USING A PANEL OF MONOCLONAL ANTIBODIES

		Monoclonal antibodies and their specificities			*IL-2 receptor expressing cells Ox 39*	*Class II expressing cells Ox 6*
	Clinical score at killing	*Total T cells rat CD5 Ox 19*	*T 'cytotoxic/ suppressor' rat CD8 OX 8*	*T 'helper' rat CD4 W3/25*		
Untreated	3	+++	++	++	+	++++
	2.5	+++	+	+	+	++++
	1	++	+	+	+	+++
	0.5	++	+	+	+	++
	0.5	++	+	+	0	++
	2	+	+	+	0	++
Quinidine treated	0.5	+	+	+	0	++
	0.5	0	0	0	0	+
	0.5	0	0	0	0	+
	0	0	0	0	0	+
	1	+	0	+	0	++

Rats were killed on day 16 after induction of EAN and sections of sciatic nerves were stained histochemically. Each row shows observations from 1 animal. Results are expressed as the average number of stained cells per visual field at magnification of ×100 read along the whole longitudinal section of sciatic nerve. For W3/25 which labels both T 'helper' cells and macrophages only cells with lymphocyte-like morphology were counted. Symbols represent the following number of stained cells: 0 = no cells, + = 1–3 cells, ++ = 4–8 cells, +++ = 9–40 cells, ++++ = >40 cells. For evaluation of clinical score *see* Material and Methods.

showed equal clinical signs and changes of body weight compared with control EAN rats (data not shown) when the highest tolerated dosage of the drug was used (1 mg per injection).

Immunohistochemical evaluation of sciatic nerve inflammation

The degee of sciatic nerve inflammation was studied in order to see whether quinidine affects T cell infiltration of target tissue or exerts its effect independently of such infiltration. For all of the T cell subsets determined, i.e., CD5$^+$ T cells, T 'cytotoxic/suppressor' cells, T 'helper' cells and IL-2 receptor expressing cells, conspicuously more infiltrating cells were observed in untreated EAN rats than in quinidine treated (Table 1). Similarly, the degree of class II transplantation antigen expression on various cell types of the sciatic nerve differed considerably between the two groups.

Neurophysiological recordings

During the course of EAN the latencies to muscle response on distal stimulation increased significantly ($P < 0.05$) in the untreated group but remained unchanged in the quinidine-treated group. The amplitudes of the muscle response were reduced in both groups, but more in the untreated group ($P < 0.001$ vs $P < 0.05$). The amplitude ratios and the duration of the muscle response remained unchanged in both groups (Table 2). After single injections of the ion channel blockers quinidine, verapamil and 4AP,

TABLE 2. NEUROPHYSIOLOGICAL MEASUREMENTS IN UNTREATED AND QUINIDINE-TREATED EAN RATS

	Before immunization *day 0, n = 4*	*EAN untreated* *day 14, n = 4*	*EAN quinidine-treated* *day 14, n = 6*
PSL (ms)	3.36±0.55	3.85±0.89, n.s.	3.03±0.24, n.s.
DSL (ms)	2.59±0.60	3.12±0.77, $p < 0.05$	2.23±0.26, n.s.
PSA (mV)	9.57±3.92	1.05±1.03, $p < 0.001$	2.99±2.54, n.s.
DSA (mV)	9.95±4.72	1.13±1.12, $p < 0.001$	3.41±3.07, $p < 0.05$
AR	0.90±0.15	0.92±0.11, n.s.	0.90±0.12, n.s.
PSD (ms)	2.95±0.58	3.25±0.80, n.s.	3.25±0.36, n.s.
DSD (ms)	2.94±0.73	3.18±0.85, n.s.	3.00±0.64, n.s.

Sciatic nerves were stimulated at the sciatic notch (proximal) and at the knee (distal). Values are expressed as mean ± SD. For statistical analysis of intraindividual differences between day 0 and day 14, the t test for paired observations was used. PSL = proximal stimulation latency, DSL = distal stimulation latency, PSA = proximal stimulation amplitude, DSA = distal stimulation amplitude, AR = amplitude ratio (proximal/distal), PSD = proximal duration, DSD = distal stimulation duration of the muscle response.

respectively, into untreated EAN rats at day 14 after immunization, a slight tendency for increased latencies and durations of muscle response on proximal and distal stimulation was observed after injection of 4AP only (Table 3). The amplitudes of the muscle responses were not obviously affected (data not shown).

Lymphocyte proliferation in vitro

Both the ion channel blockers quinidine and verapamil caused a dose-dependent biphasic modulation of antigen-induced lymphocyte proliferation irrespective of previous in vivo treatment with the channel blockers (fig. 3). The response to BPM as well as to PPD was suppressed by quinidine of concentrations above 10^{-5} M and by verapamil at concentration above 10^{-6} M in all experiments. A slightly enhanced response was observed at concentrations of 10^{-6} M of both drugs except anti-BPM response in control EAN rats. There was a tendency for suppression of BPM induced proliferation at lower blocker concentrations compared with the PPD response.

The effect on spontaneous lymphocyte proliferation in vitro of quinidine and verapamil has been tested by assessing the ^{3}H-thymidine incorporation of LNC from EAN control rats during the first 24 h of culture (Table 4). Solutions of 10^{-4} M of both drugs reduced the background values by approximately 50%, whereas lower concentrations had no influence.

To exclude the possibility of a cellular toxicity of the used drugs as an explanation for the suppressed proliferation, the tumour-promoting phorbol ester TPA, known to bypass the diacylglycerol-dependent pathway of cell activation (Truneh *et al.*, 1985), was applied at different dilutions in parallel with suppressive concentrations of quinidine and verapamil (Table 5). Blocker-induced suppression was overcome by this procedure as exemplified in the anti-PPD response.

TABLE 3. NEUROPHYSIOLOGICAL EFFECTS OF SINGLE INTRAPERITONEAL INJECTIONS OF ION CHANNEL BLOCKERS QUINIDINE (4 mg), VERAPAMIL (1 mg), AND 4-AMINO-PYRIDINE (4-AP, 1 mg) AT DAY 14 AFTER INDUCTION OF EAN

		0 min	*10 min*	*30 min*
△ PSL (%)	Quinidine	156	163	166
		81	94	100
Verapamil		94	94	94
		100	110	117
	4-AP	162	159	172
		117	111	131
△ DSL (%)	Quinidine	174	191	200
		130	104	117
	Verapamil	109	118	109
		100	111	118
	4-AP	154	154	169
		129	125	146
△ PSD (%)	Quinidine	95	113	118
		96	115	108
	Verapamil	78	83	78
		188	208	216
	4-AP	125	117	150
		126	152	152
△ DSD (%)	Quinidine	144	172	192
		105	127	114
	Verapamil	60	67	62
		204	225	225
	4-AP	120	112	140
		122	152	196

Data are percentage changes in latency and duration of muscle response between day 0 and day 14 of EAN induction recorded immediately before (0 min) and 10 min, respectively, 30 min after injection of the drug. Abbreviations of parameters as in Table 2.

DISCUSSION

Previous studies on the role of ion channels in immune responses have been performed only in vitro (for review, *see* Lewis and Cahalan, 1988) and used mainly nonspecific mitogens, such lectins (Tsien *et al.*, 1982; DeCoursey *et al.*, 1984; Kuno and Gardner 1987), anti-CD3 antibodies (Nel *et al.*, 1986), and anti-immunoglobulins (MacDougall *et al.*, 1988). We have now shown that the K^+ blocker quinidine can suppress in vivo immune responses in EAN resulting in decreased clinical and neurophysiological deficits and decreased T cell infiltration into target tissue.

Theoretically there is basis for an effect of quinidine directly on nerve function and not primarily on immune response. It has been demonstrated that conduction block of peripheral rat nerves demyelinated segmentally or focally by diphtheria toxin (Sherrratt *et al.*, 1980) and lysophosphatidyl choline (Targ and Kocsis, 1985) can be overcome by blockage of voltage-dependent K^+ conductance. The K^+ ion channel blockers 4AP and tetraethylammonium (TEA) prolong action potential (Sherratt *et al.*, 1980) and increase conduction safety factor (Davis and Jacobson, 1971). Impaired nerve conduction in EAN has been reported as a result of paranodal and segmental demyelination (Cragg and Thomas, 1964; Hall, 1967) with a raised internodal conduction time (Rasminsky

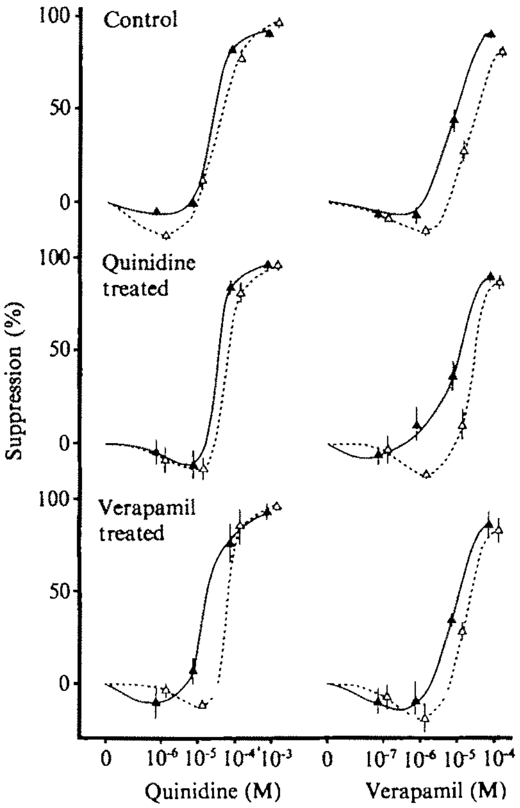

FIG. 3. Suppression of the proliferative lymphocyte response of EAN rats to the antigens BPM (filled triangles) and PPD (open triangles) by ion channel blockers quinidine and verapamil. EAN rats were treated by daily intraperitoneal injections of 4 mg quinidine and 1 mg verapamil, respectively, from the beginning of EAN induction. Control animals received 1 ml saline only. Lymph node cells were obtained on days 9–15 after EAN induction. Serial dilutions of channel blocking drugs were added at culture initiation, and ^{3}H-thymidine incorporation was measured at 3 days. The data are expressed as:

$$\% \text{ suppression} = 1 - \frac{\text{cpm of (LNC+antigen+drug)}}{\text{cpm of (LNC+antigen)}} \times 100$$

Bars represent SEM. Data refer to 4–6 experiments which were each done in triplicate. LNC = lymph node cell.

and Sumner, 1980; Lafontaine *et al.*, 1982). Demyelinated nodes expose K$^+$ channels (Bostock and Sears, 1978; Brismar, 1979) and these voltage-dependent K$^+$ channels may be overcome by the channel blockers 4AP and TE (Sherratt *et al.*, 1980; Bostock *et al.*, 1981). EAN, however, has not previously been studied in this respect. A direct effect of quinidine on nerve function in vivo seems to be of minor importance compared with the immunosuppressive effect. First, single intraperitoneal injections did not improve but instead impaired nerve function in our model system as demonstrated by prolonged latencies and durations of muscle response on proximal and distal stimulation of the sciatic nerve. Secondly, T cell infiltration into target tissue was less pronounced in long-term treated EAN rats as compared with untreated control EAN rats. Thirdly, in vitro

TABLE 4. EFFECT OF ION CHANNEL BLOCKERS QUINIDINE AND VERAPAMIL ON THE LYMPHOCYTE PROLIFERATION OF EAN RATS IN VITRO

Blocker	*^{3}H-thymidine incorporation (cpm)*	*Inhibition (%)*
None	15 928 ± 319	
Quinidine 10^{-4} M	8 970 ± 260	43.7
10^{-5} M	15 246 ± 154	4.3
Verapamil 10^{-4} M	6 528 ± 398	59.0
10^{-5} M	17 350 ± 2 605	−8.9

Lymphocytes were prepared from regional lymph nodes on day 16 after induction of EAN and incubated with respective blocker or medium alone for 24 h. ^{3}H-thymidine was present throughout the time of incubation. Results are expressed as mean ± SD of triplicates. Inhibition refers to ^{3}H-thymidine incorporation in cultures with medium alone.

TABLE 5. MODULATION IN THE IN VITRO PROLIFERATIVE RESPONSE TO PPD OF LYMPHOCYTES FROM EAN RATS BY SIMULTANEOUS INCUBATION WITH ION CHANNEL BLOCKERS AND PHORBOL ESTER (TPA)

Blocker	*TPA conc.*	*^{3}H-thymidine incorporation (cpm)*	*Inhibition (%)*
None	0	10 416 ± 446	
Quinidine 10^{-4} M	0	1 887 ± 550	81.9
	10^{-8} M	12 536 ± 847	−20.4
	10^{-7} M	16 049 ± 455	−54.1
	10^{-6} M	18 629 ± 666	−78.8
Verapamil 10^{-4} M	0	737 ± 22	92.9
	10^{-8} M	11 438 ± 545	− 9.8
	10^{-7} M	12 689 ± 1 247	−21.8
	10^{-6} M	13 885 ± 1 510	−33.3

Lymphocytes were prepared from regional lymph nodes on day 16 after induction of EAN and incubated simultaneously with PPD and ion channel blockers quinidine and verapamil, respectively, in the absence and presence of TPA as indicated. ^{3}H-thymidine was added 16 h before harvest of 3 day cultures. Results are expressed as mean ± SD of triplicates. Inhibition refers to ^{3}H-thymidine incorporation in cultures with antigen alone.

proliferative responses of lymphocytes to the neuritogenic antigen BPM were strikingly reduced by quinidine in vitro.

Although the Ca^{++} channel blocker verapamil inhibits the in vitro antigen-specific lymphocyte proliferation to a similar extent as quinidine, it did not alter the clinical course of EAN when applied in vivo. First this may be due to the in vivo concentration of verapamil being too low; an increase in daily dose from 1 to 2 mg was not tolerated. Secondly, there may be differences in bioavailability of the drugs, preventing the required concentration of verapamil at sites of action of immunosuppressive effects. Thirdly, the effect of Ca^{++} channel blockers may be more complex than those of selective K^{+} channel blockers, since Ca^{++} channel blockers decrease $[Ca^{++}{}_{I}]$, which facilitates K^{+} channel gating (Bubien *et al.*, 1988) and may in turn enhance cell activation instead of suppressing it in a certain concentration range.

Although the basic mechanism of quinidine action on ion channel gating is more selective and restricted compared with verapamil, quinidine may still influence diverse functions of immune cells, that is, processing of antigen by macrophage/dendritic cells, proliferation of lymphocytes, and effector functions of different mononuclear cells. Evidence comes from the following findings. K^+ channels are involved in macrophage activation and function of phagocytes (Gallin, 1986). Critical steps in T cell proliferation are tightly linked to K^+ channel gating (Nel *et al.*, 1987; Lewis and Cahalan, 1988). B cell proliferation and antibody production are inhibited by K^+ channel blockers (Sutro *et al.*, 1988). T cell and natural killer cell cytoxicity are dependent on K^+ channel activation (Schlichter *et al.*, 1986; Lewis and Cahalan, 1988). We show the in vitro lymphocyte proliferation in response to the relevant autoantigen is strikingly inhibited in a dose-dependent manner by the K^+ channel blocker quinidine. The spontaneous proliferation was also reduced to a somewhat lower extent. Interestingly, there is recent evidence that the signals mediating T cell proliferation, at least in model systems of cytotoxic T cell clones, are identical to those mediating cytotoxicity and can be bypassed by phorbol esters (Treves *et al.*, 1987). The molecular events involved in quinidine suppression of immune responses remain to be clarified. The present data showing that TPA can overcome the quinidine-induced blocking effect argues against a quinidine action on the protein kinase C-dependent pathway.

In summary, the suppression of EAN by quinidine treatment is caused primarily by an inhibition of myelin driven autoimmune responses. This result may have implications for clinical practice, since quinidine is used in non-immune-mediated diseases and might give immunomodulatory side effects. Furthermore, beneficial effects of K^+ channel blocking drugs in immune-mediated disease, such as multiple sclerosis (Jones *et al.*, 1983; Stefoski *et al.*, 1987), the Guillain-Barré and Lambert-Eaton syndromes (Lundh *et al.*, 1977), and myasthenia gravis (Lundh *et al.*, 1979), should be explored not only on the basis of their influence on nerve function, but also for their immunomodulatory potency. Studies employing K^+ channel blockers therapeutically after the onset of clinical signs are now warranted in experimental models of these diseases.

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THE NATURAL HISTORY OF MULTIPLE SCLEROSIS: A GEOGRAPHICALLY BASED STUDY

2. PREDICTIVE VALUE OF THE EARLY CLINICAL COURSE

by B. G. WEINSHENKER, B. BASS, G. P. A. RICE, J. NOSEWORTHY, W. CARRIERE, J. BASKERVILLE *and* G. C. EBERS

(*From the Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada*)

SUMMARY

Controversy exists regarding the predictive value of the early clinical course of multiple sclerosis (MS). Three parameters often considered are the attack rate, the first interattack interval and the rate at which disability develops in the early years of the disease. We have recorded the time to reach successive levels of disability defined by the Kurtzke Disability Status Scale (DSS) in 1,099 MS patients followed at University Hospital, London, Canada between 1972 and 1984. Our population is particularly suitable because of its size, the high degree of ascertainment of cases in the community, and the regular follow-up provided. Life table analysis was used to compare survival in patients stratified according to the above three parameters using DSS 6 as end point. Significant differences were evident in the survival distributions. Despite the extensive interindividual variation in the rate at which disability developed, the early course of MS may be useful in determining the relative risk of rapid progression.

INTRODUCTION

To conduct appropriate clinical therapeutic trials of potentially toxic immunosuppressive agents in multiple sclerosis (MS), an investigator strives to select those patients who are expected to suffer rapid, if not continuous, neurological deterioration. The approach of selecting patients with 'progressive MS' is based on generally accepted beliefs, supported by some data which suggest that these patients have a poor outcome (Leibowitz and Alter, 1970; Kurtzke *et al.*, 1977; Confavreux *et al.*, 1980; Poser *et al.*, 1983; Verjans *et al.*, 1983). Kurtzke *et al.* (1977) have pointed out the difficulties in using a retrospectively made pronouncement for prospective decisions in patient care. Other parameters which reflect the early course of MS would be more desirable as prognostic indices. Many studies have failed to document any relationship between the number of attacks in the early years of MS and outcome (Fog and Linnemann, 1970; Kurtzke *et al.*, 1977; Patzold and Pocklington, 1982). The potential predictive value of early onset of moderate neurological disability has been addressed by relatively few authors, although Kurtzke *et al.* (1977) found disability 5 yrs after onset of MS to be the most useful parameter.

We have analysed the predictive value of a number of parameters which reflect the early course of MS in a longitudinally evaluated population of MS patients followed

Correspondence to: Dr G. C. Ebers, Department of Clinical Neurological Sciences, University Hospital, 339 Windermere Road, London, Ontario N6A 5A5, Canada.

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in London, Canada; these include the frequency of attacks in the first 2 yrs of MS, the interval between the first and second attack and the rate at which moderate disability (level 3 on the Kurtzke Disability Status Scale (DSS)) was reached. Outcome was assessed by the number of years to reach level 6 on the DSS.

METHODS

Data base

The London MS clinic provides ongoing follow-up to MS patients in its geographic base of southern Ontario. It retains the characteristics of both a tertiary referral centre for the province of Ontario and a geographically-based clinic in Middlesex county. A prevalence survey of MS in Middlesex county indicated that 90% of patients with MS were followed by our clinic (Hader *et al.*, 1988). Between 1979 and 1984, we reviewed data collected on 1,099 consecutive patients evaluated between 1972 and 1984. The details of the data collected and its analysis have been described previously, along with the demographics, clinical course and the progress of disability as a function of time (Weinshenker *et al.*, 1989). We analysed separately the data on an 'incidence' subset of 197 patients who were seen by a neurologist within 1 yr from onset of MS. Patients were not treated with specific therapy for MS other than corticosteroids for acute exacerbations. Data were recorded on standardized forms and entered onto a mainframe computer.

Definitions

The onset of MS was taken to be the date of occurrence of the first unequivocal symptoms of MS. An attack was defined as acute development of new symptoms or worsening of existing symptoms, the duration of which was greater than 24 h (Poser *et al.*, 1983). The attack frequency could only be determined retrospectively for most patients in the total population so that this definition could be used only as a working guideline. Generally, attack frequency was recorded prospectively for the 'seen from onset' subgroup. Disability that had developed before attendance in our clinic was determined historically for most patients based on patient interview and review of their records; however, in the 'seen from onset' subgroup disability was analysed prospectively. Disability was graded according to the DSS (Kurtzke, 1961).

Analysis

Patients with adequately determined disability time data and with recorded values for the independent variables considered were stratified as indicated in Table 1. Life table survival analysis of disability was performed using the statistical program SAS (SAS Institute Inc., Cary, North Carolina). We compared survival curves of the total population and the 'seen from onset' subgroups stratified according to (1) numbers of attacks in the first 2 yrs from onset of MS, (2) the interval between the first and second attack of MS, and (3) the duration from onset of MS at which DSS 3 was reached. In considering the effect of attack frequency and first interattack interval, patients with progressive disease from onset were eliminated as these patients did not have discrete attacks.

When studying the effect of differences in the time to reach DSS 3, the duration of MS until DSS 6 was reached was adjusted to the time interval from reaching DSS 3, so as to render these parameters independent of one another. Similarly, the duration of MS was indexed to the time from the second attack of MS when studying the effect of the first interattack interval. Generally, the population was divided in such a way as to create equal sample sizes, although additional stratifications were used where it was felt that these were clinically relevant. The significance of differences between the survival curves was tested with the logrank statistic (Kalbfleisch and Prentice, 1980). DSS 6 was chosen as end point as it is generally considered to reflect severe disability, and a sufficiently large number of patients reached DSS 6 to permit useful analysis.

The variation in the dependent variable, time to reach DSS 6, that was unaccounted for by stratification according to the three independent variables was assessed by scatter plots.

TABLE 1. STRATIFICATION OF PATIENTS

			n
Total population			
No. of attacks in first 2 years*	Low	0−1	452
	Intermediate	2−4	244
	High	≥5	34
First interattack interval (yrs)*	Short	0−2	425
	Intermediate	3−5	153
	Long	≥6	174
Time to reach DSS 3 (yrs)	Short	0−2	209
	Intermediate	3−7	239
	Long	≥8	226
'Seen from onset' subgroup			
No. of attacks in first 2 years*	Low	0−2	77
	Intermediate	3−4	35
	High	≥5	16
First interattack interval (yrs)*	Short	0−1	109
	Long	≥2	39
Time to reach DSS 3 (yrs)	Short	0−2	44
	Long	≥3	27

* Patients with chronically progressive MS were excluded.

TABLE 2. ATTACK FREQUENCY (MEAN ± SEM)

	Total population (n)	*'Seen from onset' (n)*
First year after onset		
RR	1.57±0.05 (358)	1.80±0.10 (119)
RR → P	1.28±0.05 (272)	2.08±0.22 (25)
RP	1.42±0.06 (132)	2.33±0.37 (9)
Second year after onset		
RR	0.35±0.04 (322)	0.55±0.08 (99)
RR → P	0.40±0.06 (255)	1.08±0.22 (24)
RP	0.48±0.07 (119)	1.43±0.37 (7)

RR = relapsing and remitting; RR → P = remitting and subsequently progressive; RP = progressive from onset with superimposed attacks; n = no. of patients with available data.

RESULTS

Distribution of predictive parameters within the population

The frequency distribution of the three variables was highly skewed to the right. The attack frequency according to clinical course is shown in Table 2. The relatively higher frequency of attacks recorded in the 'seen from onset' population as compared with the total population is likely to be attributable to the prospective way in which the data were collected in that subgroup; this is similar to the findings of others who have compared retrospectively and prospectively ascertained attack frequencies (Fog and Linnemann, 1970; Patzold and Pocklington, 1982). Furthermore, there is an inherent bias in the definition of this subgroup towards patients who had an acute attack at onset.

The median first interattack interval was 2 yrs (range 1−34) for the total population and 1 yr (range 1−7) for the 'seen from onset' subgroup. The difference is best explained by

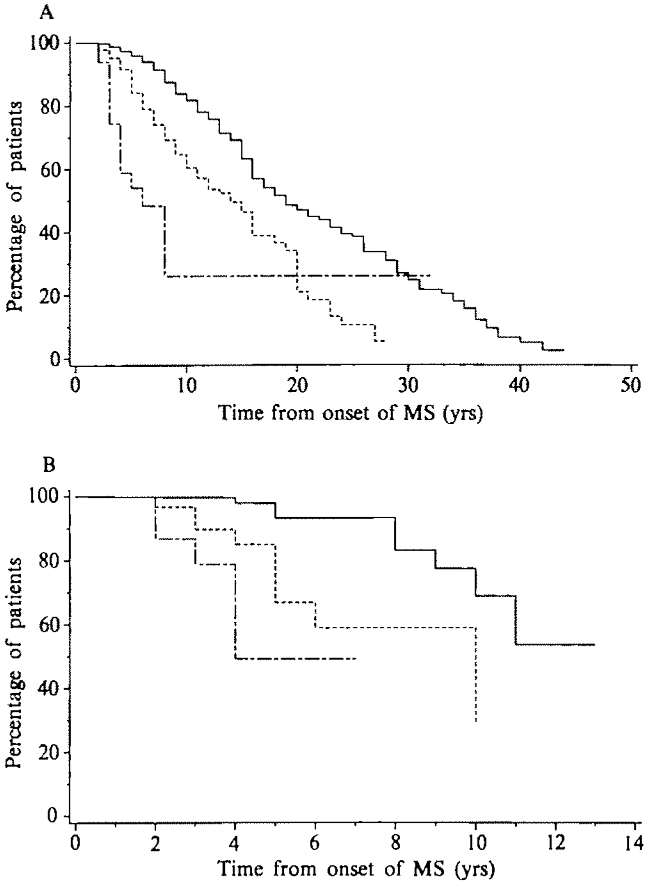

FIG. 1. Actuarial analysis of disability: A, in the total population; B, in the 'seen from onset' subgroup. The percentage of patients not having reached DSS 6 is shown after stratification according to the number of attacks in the first 2 yrs from onset of MS. The difference between the groups is significant ($P < 0.0001$). —— (low); - - - - (intermediate); —— (high).

the limited follow-up available in the 'seen from onset' subgroup (follow-up 4.2 ± 0.2 yrs, mean ± SEM) which necessarily excludes patients who have a long first interattack interval. Inherent differences between retrospective and prospective methods of data collection probably also play a role.

Among those patients who reached DSS 3, the median interval from onset of MS to reach that level of disability was 4 yrs for the total population and 2 yrs for the 'seen from onset' subgroup. Data were available for a significantly smaller percentage of patients in the latter than in the former (37.1% vs 62.4%), largely due to the differences in duration of follow-up and the resulting difference in the percentage that reached DSS 3.

Predictive value of parameters reflecting the early course of MS

Survival curves stratified as indicated in Table 1 are shown in figs 1–3 using DSS 6 as endpoint. Significant differences were evident both for the total population for number

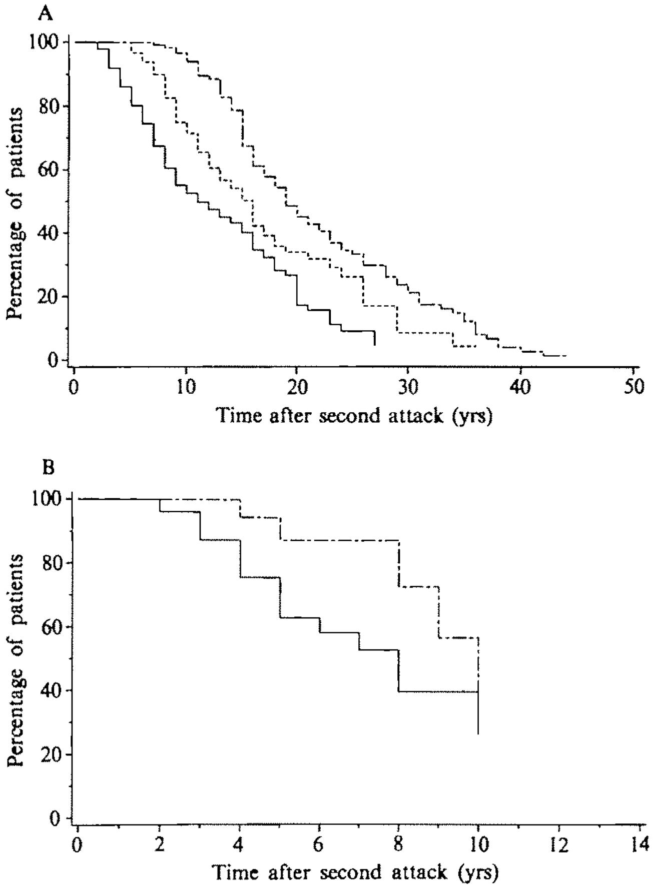

FIG. 2. Actuarial anlaysis of disability: A, in the total population; B in the 'seen from onset' subgroup. Stratification is done according to the first interattack interval and time is indexed from the second attack. The difference between the groups is significant for the total population ($P < 0.0001$ for the total population and $P = 0.09$ for the 'seen from onset' subgroup). —— (short); - - - - (intermediate); —— (long).

of attacks in the first 2 yrs, first interattack interval and time to reach DSS 3. The differences were significant in the 'seen from onset' subgroup for number of attacks in the first 2 yrs and time to reach DSS 3. Where a small number of patients comprised a given subgroup, as in patients with 5 or more attacks in the first 2 yrs (fig. 1A), the length of 'steps' in the survival curve was long. Furthermore, these survival analyses do not account for differences in the rate at which more advanced levels of disability were reached; however, similar results were obtained when studying the effect of the same three variables on survival using DSS 8 as endpoint (data not shown).

Variability among individuals

A scatter plot of the time to reach DSS 6 after DSS 3 was reached is shown in fig. 4 for the total population who had reached DSS 6. Similar scatter plots are shown in

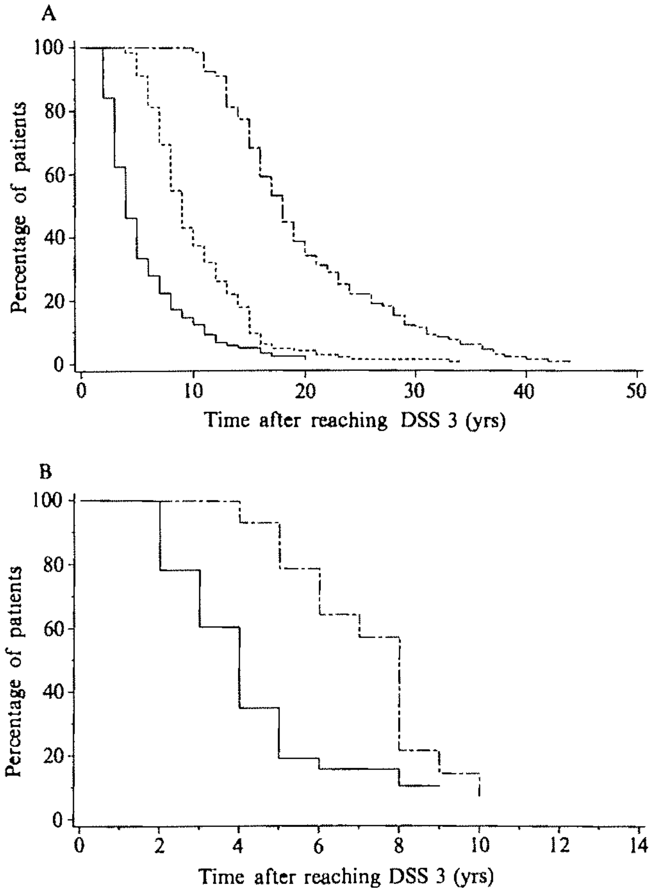

FIG. 3. Actuarial analysis of disability: A, in the total population; B in the 'seen from onset' subgroup. Stratification is done according to the time to reach moderate disability (DSS 3). Time is indexed from when DSS 3 is reached. The difference between the groups is significant ($P < 0.0001$). —— (short); - - - - (intermediate); —— (long).

figs 5 and 6 stratified according to numbers of attacks in the first 2 yrs following onset of MS and the first interattack interval. It is clear that there is a large degree of interindividual variability in the course of MS that is unaccounted for by each of these variables independently. These figures also demonstrate the skew to the right in frequency distribution of the 3 independent variables considered.

DISCUSSION

As we have previously reviewed, considerable variation, from 0.1 to 1 attack per yr, exists in the reported average attack frequency in MS (Weinshenker and Ebers, 1987). This is partly related to the period over which attacks of MS are counted. There is general consensus that attack frequency of MS lessens with time (McAlpine and Compston, 1952; Panelius, 1969; Broman *et al.*, 1981; Patzold and Pocklington, 1982). The period

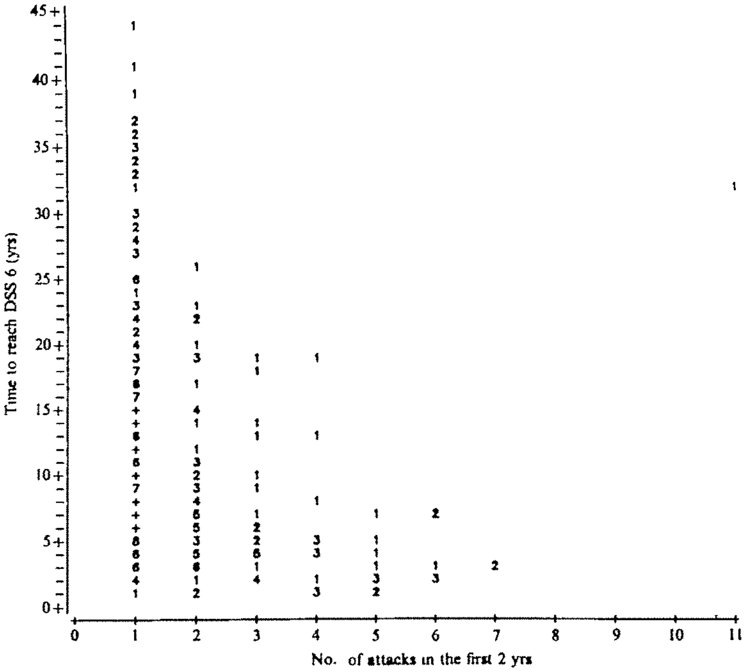

FIG. 4. Scatter plot of time to reach DSS 6 from onset of MS versus the number of attacks in the first 2 yrs after onset of MS. + = more than 10 observations at this point.

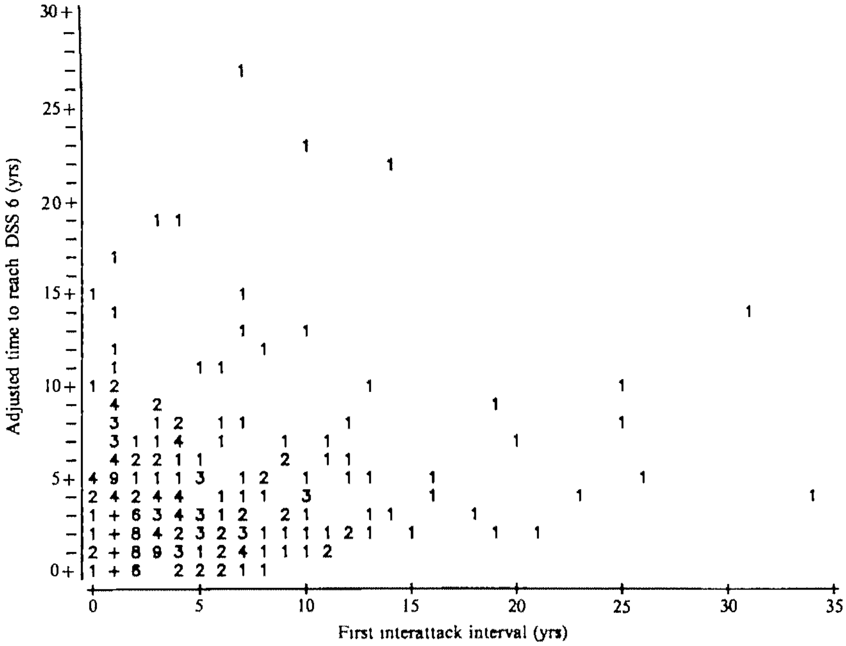

FIG. 5. Scatter plot of time to reach DSS 6 (adjusted to the time following the second attack) versus the first interattack interval. + = more than 10 observations at this point.

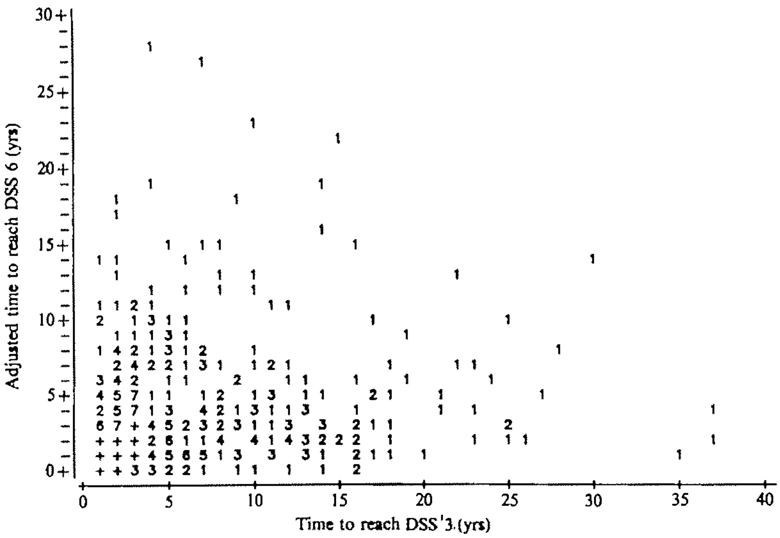

FIG. 6. Scatter plot of time to reach DSS 6 (adjusted to the time after DSS 3 is reached) versus the time to reach DSS 3. + = more than 10 observations at this point.

over which attack frequency is studied relative to the overall course of MS must therefore be consistent among patients. Other factors such as age at onset and sex have also been suggested to influence attack rates (Broman *et al.*, 1981; Patzold and Pockington, 1982). Furthermore, a significant discrepancy exists between retrospectively and prospectively obtained attack rates (Fog and Linnemann, 1970; Patzold and Pocklington, 1982). Our data corroborate the findings of others, in that we recorded a greater number of attacks in the 'seen from onset' subgroup ('prospective') in the first 2 yrs of disease than in the total population.

Other investigators have not found that attack frequency predicted outcome. Confavreux *et al.* (1980) in their study of 349 patients in Lyon, France, found that the number of relapses was greater for benign than for more malignant MS; however, the mean duration between the first and second relapse was approximately 6 yrs in 'benign' and 'intermediate' cases (defined by the rate at which disability developed) compared with 0.9 yrs in 'hyperacute' and 2.4 yrs in 'acute' cases. Kurtzke *et al.* (1977) found no dissociation between attack frequency in the first 5 yrs and disability status at 10 or 15 yrs. Fog and Linnemann (1970) and Patzold and Pocklington (1982) found no correlation of disease progression and relapse rate. However, follow-up was only 3.5 yrs on average in the former series, and in both of these studies progression was indexed to the period of observation rather than to the entire course from onset of MS. The populations studied were not geographically based and treatment may have altered outcome in selected cases in the former series.

We suspect that failure to detect a positive association between attack frequency and outcome could have resulted from (1) failing to separate data for patients with progressive disease from onset, who have poor outcome yet have few if any discrete attacks, (2) failure to analyse the effect of attack rate in the early years of disease rather than attack rate averaged over the entire duration of MS, and (3) lack of prospective information.

Kurtzke *et al.* (1977) reported that the disability status at 5 yrs from diagnosis predicted disability at 10 and 15 yrs in a US World War II cohort. Surprisingly, however, 12% and 16% of severely disabled patients at diagnosis had only mild disability at 10 and 15 yrs from diagnosis, respectively. These results probably result from collection of data from traditional medical records, which document evaluations conducted at the time of exacerbations which most often do not reflect permanent disability.

We find significant differences in survival curves of disability (DSS 6) between patients with high or low number of attacks in the first 2 yrs after onset of MS, a short or long first interattack interval and a short or long time to reach DSS 3. Similar results were found when the data were similarly analysed using DSS 8 as endpoint. DSS 6 was reached earlier in patients with a higher number of attacks, shorter first interattack interval and a shorter time to reach DSS 3. Our data, unlike those of previous investigators, quantitate the magnitude of the differences between high and low attack groups. The substantial overlap of time to DSS 6 between groups of patients stratified according to each of the independent variables can be accounted for in two ways. First, the scatter plot, unlike the survival analysis, fails to account for censoring of patients who did not reach the endpoint over the period of follow-up. Secondly, despite overall association of each independent variable with outcome, considerable interindividual variation renders univariate analysis of limited value.

We are currently examining the association of outcome with demographic and clinical factors (age at onset, sex, initial symptomatology). A hierarchical multivariate analysis of prognostic indices will be used beginning with demographic and clinical factors that can be determined at onset of disease. Predictions are subsequently modified by observations of the early course of MS. Predictive models based on these indices will have greatest value in defining groups for study in clinical trials, rather than in determining the prognosis for individuals, given the large interindividual differences in the pace of the disease.

To date, no evidence has been presented to indicate that the treatment of acute attacks ameliorates the outcome of MS (Matthews, 1985), although the studies supporting the lack of long-term benefit may suffer from inadequate power to answer this issue. It will be of considerable importance to determine if agents such as alpha interferon (Panitch, 1987) or copolymer I (Bornstein *et al.*, 1987), which appear to decrease the attack frequency in MS, improve outcome.

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POLYNEUROPATHY IN FELINE NIEMANN-PICK DISEASE

by PAUL A. CUDDON,[1] ROBERT J. HIGGINS,[2] IAN D. DUNCAN,[1]
STEPHEN P. F. MILLER,[3] JOANE M. PARENT[4] *and* ANN B. MOSER[5]

(From the [1]School of Veterinary Medicine, University of Wisconsin, Madison, WI, [2]School of Veterinary Medicine, University of California-Davis, Davis, CA, [3]National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, MD, USA, [4]Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada and [5]Kennedy Institute for Handicapped Children, Baltimore, MD, USA)

SUMMARY

Two related cats, aged 5 months and 7 months, and 1 unrelated cat, aged 4 months, presented with signs of a progressive neuromuscular disease. Detailed electrophysiological studies suggested a primary demyelinating polyneuropathy, which was confirmed by muscle and nerve biopsies and on necropsy examination. Light and electron microscopic findings indicated a lysosomal storage disease, which was diagnosed as sphingomyelinase deficiency (Niemann-Pick disease) by enzyme analysis and lipid fractionation, although significant biochemical differences existed between the 2 related cats and the third cat. Several lines of evidence suggest that these 2 related cats were affected with a variant of type A Niemann-Pick disease, whereas cat 3 represented classic Niemann-Pick disease type A.

INTRODUCTION

Niemann-Pick disease is a lysosomal storage disease inherited as an autosomal recessive trait and characterized by the accumulation of sphingomyelin and other lipids (cholesterol, gangliosides GM_2 and GM_3, and the acidic glycerolipid, bis(monoacylglyceryl) phosphate) in neurons and cells of the mononuclear phagocyte system (Wenger *et al.*, 1980; Snyder *et al.*, 1982; Brady, 1983). The metabolic defect is a marked or total absence of sphingomyelinase which catalyses the hydrolysis of sphingomyelin to ceramide and phosphorylcholine (Brady, 1983). Sphingomyelin has been recognized as a constituent of the plasma membrane and many intracellular organelles of all cells, and as one of the major lipids of myelin (Brady, 1983; Kudoh *et al.*, 1983). Six variants of Niemann-Pick disease have been described in man (types A–F). This division is based on the age of onset and progression of the disease, the extent of brain and spinal cord involvement, the severity of hepatosplenomegaly and the degree of sphingomyelinase activity in homozygotes and heterozygotes (Schneider *et al.*, 1978; Brady, 1983; Thomas, 1984). Niemann-Pick disease in animals, a syndrome analogous to the Type A variant, has been reported in Siamese cats (Chrisp *et al.*, 1970; Wenger *et al.*, 1980; Snyder *et al.*, 1982), a domestic shorthaired cat (Percy and Jortner, 1971), a Balinese cat (Baker

Correspondence to: Dr Paul Cuddon, Department of Medical Sciences, School of Veterinary Medicine, 2015 Linden Drive West, University of Wisconsin, Madison, WI 53706, USA.

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et al., 1987), a miniature poodle dog (Bundza *et al.*, 1979), and 2 mutant strains of mice (Miyawaki *et al.*, 1982; Sakiyama *et al.*, 1982). The type C variant has also been described in a strain of mice (Pentchev *et al.*, 1980). The classic neurological signs in the animals with type A Niemann-Pick disease, starting at 3−5 months of age, were retarded growth and learning ability, obtundation, nystagmus, continuous coarse head tremors, ataxia, incoordination, hypermetria and paresis. Limb weakness was not a consistent or major clinical finding, and was not linked to peripheral nerve involvement (Wenger *et al.*, 1980; Snyder *et al.*, 1982). Descriptions of peripheral nerve involvement in Niemann-Pick disease type A in man have also been scarce (Gumbinas *et al.*, 1975; Brady, 1983; Landrieu and Saïd, 1984). This paper describes Niemann-Pick disease in cats with clinical signs primarily referrable to the peripheral nervous system. Because of biochemical differences between Cats 1 and 2 and a third cat (Cat 3), which displayed the classic type A Niemann-Pick disease phenotype, we suggest that Cats 1 and 2 may represent a new variant of type A Niemann-Pick disease. This is supported by the absence of a detectable sphingomyelinase deficiency in at least 1 known heterozygote of the first 2 cats.

MATERIAL AND METHODS

Cat 1

A 5-month-old, 1818 g intact male Red Point Siamese cat was presented to the Veterinary Medical Teaching Hospital, Davis, California, with a 2-month history of progressive tetraparesis and ataxia, inability to jump, voice change and poor growth. Neurological examination revealed a severely paretic/ataxic gait with a pronounced palmigrade/plantigrade stance; severe proprioceptive and postural reaction deficits in all limbs, although significantly worse in the forelimbs; hyporeflexic to absent patellar, biceps and triceps reflexes; hypotonia, and decreased withdrawal and panniculus reflexes despite normal pain sensation. Perineal reflexes, urination, defaecation and cranial nerve examination were normal. There was no significant muscle atrophy.

Cat 2

A 7-month-old, 2045 g intact male Black Oriental Shorthair cat was presented to the Western College of Veterinary Medicine, Saskatoon, Canada, with a 2-month history of progressive tetraparesis and ataxia. This cat was one of the offspring of a mating involving a full sister of Cat 1. There was a similar history of poor growth from birth and during the week before admission, the cat had developed a noticeable fine head tremor. Neurological examination showed almost identical abnormalities to the first cat. However, unlike Cat 1, nociceptive reflexes (withdrawals) and the panniculus reflex were within normal limits.

Cat 3

A 4-month-old, 2273 g intact male Siamese cat was presented to the Veterinary Medical Teaching Hospital, Madison, Wisconsin, with a 2½-month progressive history of tremors in both hindlimbs and tail and to a lesser extent in both forelimbs, especially when walking. The only other neurological abnormality noted was a mild bilateral decrease in patellar reflexes. The cat deteriorated neurologically over the next 10 months with significant worsening of the body tremors to the point where it was unable to walk more than a few steps before falling. The hindlimb gait had become more plantigrade. Patellar reflexes had become almost undetectable, and postural reactions were poor in all four limbs. Moderate generalized muscle atrophy was present. A mild head tremor had also developed at this time.

In summary, all cats were assessed to have a polyneuropathy with tetraparesis, hypotonia and hyporeflexia. Cats 2 and 3 also showed mild cerebellar involvement.

Laboratory data

On admission, a complete blood count, biochemical profile and urinalysis were obtained in each cat. In addition, a feline leukemia virus ELISA test (all 3 cats); cerebrospinal fluid (CSF) analysis (Cats 2 and 3) and a bone marrow aspirate (Cat 3) were performed.

Electrophysiology

Electromyography and measurements of motor and sensory nerve conduction velocity were performed on all 3 cats under general anaesthesia (Ribelin and Leswing, 1968; Duncan, 1980; Redding and Ingram, 1984).

Muscle and nerve histochemistry

Quadriceps muscle biopsies were collected surgically from all cats and routinely processed (Cardinet and Holliday, 1979). Histological evaluation included specific studies with haematoxylin and eosin (HE) modified trichrome, periodic acid-Schiff (PAS) haematoxylin, acid and alkaline phosphatase, myofibrillar ATPase following preincubation at pH 9.8 and 4.3 and nonspecific esterase stains. A sciatic nerve biopsy from Cat 1 was examined histochemically using HE, modified trichrome, PAS-haematoxylin, acid phosphatase, nonspecific esterase and silver stains.

Because of the progressive nature of the neurological dysfunction and the poor prognosis in all 3 cats, euthanasia was elected.

Pathology

A complete necropsy with subsequent histopathological examination of HE stained tissues was done on all cats and additionally, selected tissues were stained with PAS, toluidine blue, luxol fast blue and cresyl violet. Also selected samples of the PNS and CNS were examined ultrastructurally following routine procedures as previously described (Duncan, 1980; Higgins *et al.*, 1982).

Lysosomal enzyme analysis

A 10% homogenate solution of frozen frontal brain in double distilled water from Cat 1 was tested for activity of the following lysosomal enzymes: sphingomyelinase at pH 5.0, using bovine brain sphingomyelin as substrate, radioactively labelled to produce ^{14}C-sphingomyelin (Wenger, 1977); hexosaminidase at pH 5.4, using the substrate p-nitrophenyl β-D-N-acetyl glucosamine (O'Brien, 1983); arylsulphatase A, B and C, using the artificial substrates p-nitrocatechol sulphate and NaCl at pH 5.0, p-nitrocatechol sulphate without NaCl at pH 6.0; and p-nitrophenyl sulphate at pH 7.3, respectively (Kolodny and Moser, 1983); ceramidase at pH 4.0, using the natural radioactively labelled substrate ^{14}C-ceramide (Moser and Chen, 1983); and other lysosomal enzymes (α-iduronidase (McKusick and Neufeld, 1983), α-galactosidase (Desnick and Sweeley, 1983) and β-galactosidase (Holmes and O'Brien, 1978). Splenic tissue from Cat 3 was tested for activity of sphingomyelinase (as above); hexosaminidase using the substrate 4-MU β-D-N-acetyl glucosamine (Tallman *et al.*, 1974); and β-glucocerebrosidase using ^{14}C-β-glucocerebroside (Pentchev *et al.*, 1973).

Protein concentrations were determined by the method of Lowry using human serum albumin as the standard (Lowry *et al.*, 1951).

Lipid analysis

Total lipids were extracted from both the liver and kidney of Cat 1 and the spleen of Cat 3 and then compared with age-matched controls. The lipid extracts were fractionated either by Folch partitioning (Folch *et al.*, 1957) or by column chromatography on silica gel. Four fractions were obtained by column chromatography: cholesterol esters (fraction I); mono-, di- and triglycerides, cholesterol and ceramide (fraction II); glycolipids (fraction III); and phospholipids (fraction IV) (Vance and Sweeley, 1967). The individual lipids were quantitated by one-dimensional TLC analysis on silica gel plates, with standards in adjacent lanes. The TLC solvent systems were: A, chloroform:methanol:water (65:25:4) or B, chloroform:methanol:glacial acetic acid:water (60:40:4:2) for phospholipids, and C, hexane:diethylether: glacial acetic acid (80:20:1) for neutral lipids. After visualization by charring with 3% cupric acetate in 8% phosphoric acid (Fewster *et al.*, 1969), the spots were semi quantitated visually (Table 2, Cat 1) or quantitated by densitometry (Table 3, Cat 3). The identification of bis(monoacylglyceryl) phosphate was verified in Cat 3 by two-dimensional TLC analysis using solvent systems of D, chloroform:methanol: 29% ammonium hydroxide (65:35:5) followed by E, chloroform:acetone:methanol:glacial acetic acid:water (20:8:4:4:2) (Rouser *et al.*, 1976) with drying under a stream of nitrogen for 50 min between developments. Gangliosides were determined in brain tissue by chloroform/methanol extraction and Folch partitioning with distilled water (Folch *et al.*, 1957), followed by two reextractions of the lower phase with fresh upper phase. The lyophilized but undialysed upper phase was then dissolved in chloroform/methanol (2:1) and portions were analysed by TLC (silica gel, chloroform:methanol:0.2% aqueous calcium chloride, 60:40:10). After visualization with resorcinol (Svennerholm, 1957), the gangliosides were estimated visually (Cat 1), or scanned with a densitometer and quantitated relative to a GM_3 standard (Cat 3).

Fibroblast culture enzyme analysis

Eight related cats, including the father and grandmother of Cat 1, and a full sister of the father of Cat 2, were tested for heterozygosity for sphingomyelinase activity using cultured skin fibroblasts (Wenger, 1977).

RESULTS

Laboratory data

The results of haematology and routine urinalysis for all cats were within normal limits. However, there were mild elevations in alkaline phosphatase, cholesterol and creatine kinase. All 3 cats were negative for feline leukaemia virus. In Cats 2 and 3, CSF analysis showed a mild increase in protein (0.27 g/l and 0.37 g/l, respectively) (normal <0.25 g/l), with a normal nucleated cell count (2 cells/μl and 1 cell/μl, respectively) (normal <5 cells/μl). Occasional foamy macrophages with large irregular vacuoles containing light-blue granular material were seen. These large, round to oval macrophages were also observed in the bone marrow aspirate from Cat 3.

Electrophysiology

The most outstanding and consistent finding was a dramatic slowing of nerve conduction along motor and sensory nerves in all 3 cats (Table 1). Both motor and sensory action potentials were polyphasic and demonstrated temporal dispersion. The compound sensory action potential from the radial nerve in Cat 1 and the muscle action potential produced by proximal stimulation of the sciatic nerve in Cat 3 also showed a decrease in amplitude (Table 1, fig. 1). It was necessary to increase the stimulus intensity considerably (×10 normal) for an action potential to be visualized. Electromyography showed only mildly increased insertion activity, and variable mild spontaneous activity (fibrillation potentials and positive sharp waves) in a small number of appendicular muscles in all cats.

Muscle and nerve histochemistry

Microscopic examination of muscle biopsies in all cats did not demonstrate any evidence of denervation atrophy, as was suggested by electromyography. The only significant

TABLE 1. MOTOR AND SENSORY CONDUCTION

	Motor nerve conduction					*Sensory nerve conduction*		
	Amplitude (mV)		*Duration (ms)*		*MNCV*	*Amplitude*	*Duration*	*SNCV*
Nerve	*Proximal*	*Distal*	*Proximal*	*Distal*	*(m/s)*	*(µV)*	*(ms)*	*(m/s)*
Cat 1								
Sciatic/tibial	3.5	4.5	19.0	13.5	10.0			
Lateral superficial radial						5.0	6.0	33.9
Cat 2								
Sciatic/tibial	1.0	2.0	17.5	9.2	18.3			
Lateral superficial radial						–	–	–
Cat 3								
Sciatic/tibial	0.15	3.6	3.5	18.0	16.0			
Lateral superficial radial						–	–	–
Normals								
Sciatic/tibial*	13.7		–		91.0			
Mean (range)	(0.6–30.0)		(1–2)		(77–103)			
Lateral superficial radial**								
Mean ± SD						29.1 ± 12.4	1.6 ± 0.34	83.6 ± 8.3

* Ribelin and Leswing (1968). ** Redding and Ingram (1984). MNCV = motor nerve conduction velocity. SNCV = sensory nerve conduction velocity.

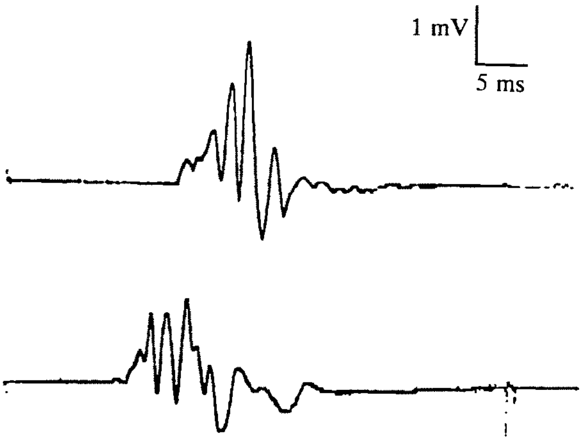

FIG. 1. Compound muscle action potentials produced by electrical stimulation at 2 separate sites along the sciatic nerve with recording from the plantar interosseus muscles. Note the significant temporal dispersion and polyphasia in each of the 2 tracings. The amplitude of both action potentials is at the low end of the range of established normal values for the cat.

finding was a number of acid phosphatase positive cells (macrophages) around the capillaries of the perimysial connective tissue.

Examination of the nerve biopsy from Cat 1 showed severe diffuse myelin degeneration with large ovoid cells lining the denuded intact axons. These cells were positive for acid phosphatase and nonspecific esterase but negative with the PAS stain. Selective silver staining of axons revealed no apparent axon loss accompanying the demyelination.

Pathological findings

No gross lesions were seen in any of the cats apart from a mild splenomegaly and moderate hepatomegaly. Histologically, there were multifocal aggregates of macrophage-like cells in the splenic white pulp, lymph nodes, lamina propria of the small and large intestine, lung, bone marrow, and in the thyroid and adrenal glands. These cells contained multiple small, variably sized, refractile and metachromatically staining granules demonstrated with toluidine blue and Giemsa stains. Similar distension and metachromasia was demonstrated in the epithelial, endothelial and mesangial cells of the renal glomeruli, the distal convoluted tubular and bile duct epithelium and in hepatocytes and Kupffer cells. The smooth muscle cells in the small intestine and the retinal ganglion cells were also involved.

CNS pathology was prominent with eccentric or concentric vacuolation and granular distension of neurons, glial cells, endothelium, choroid plexus epithelium and ependyma. Macrophages, distended with vacuoles, were widely scattered throughout the CNS parenchyma. There was variable involvement of most neurons of the cerebrum and brainstem. The cerebellar involvement was most prominent in Purkinje cells, which uniformly showed severe cytoplasmic distension. White matter tracts throughout the spinal cord showed only mild evidence of demyelination, myelin pathology and axon degeneration, which was in direct contrast to the severe demyelination observed in the PNS. Most ventral horn cells were distended with eccentrically positioned vacuoles and metachromatic granules.

In the PNS, autonomic and dorsal root ganglion cells showed the same granular and vacuolar changes as described above. There was partial to complete segmental demyelination of morphologically intact axons of the dorsal and ventral nerve roots and of cranial and spinal nerves, as well as thinly myelinated axons suggestive of remyelination. In all peripheral nerves examined, the majority of fibres were either demyelinated or remyelinating (fig. 2). The endoneurium was hypercellular with large numbers of macrophage-like cells containing intracytoplasmic myelin debris and metachromatic granules interspersed between myelinated fibres. There was a sharp demarcation of affected peripheral nerve roots at their root exit zone from the much less severely affected CNS myelinated axons. Despite the significant changes seen in both ventral horn and dorsal root ganglion cells, light microscopy revealed little evidence of peripheral axonal degeneration. The vacuolar material and granules seen in neurons, glial cells and macrophages failed to stain with PAS, luxol fast blue or cresyl violet stains.

Ultrastructural examination of the PNS revealed morphologically intact axons that

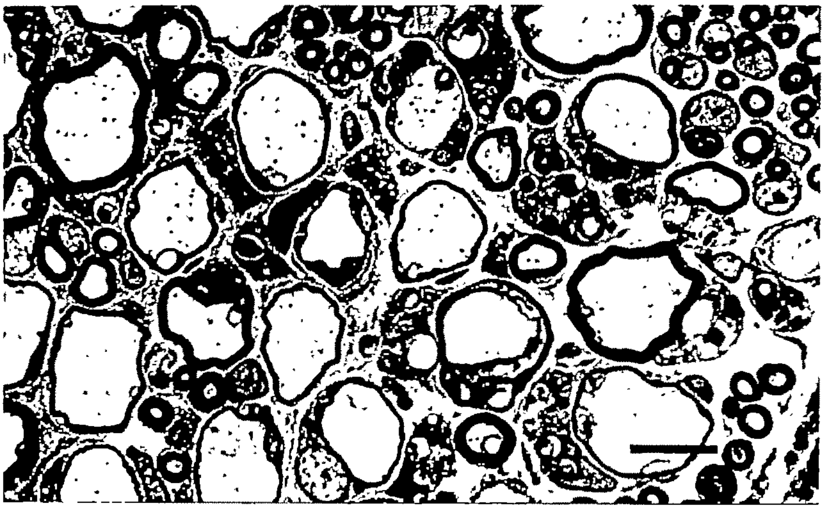

FIG. 2. Photomicrograph of a 1 μm transverse section of spinal nerve root. Note partially or completely demyelinated large diameter axons surrounded by macrophages and other thinly myelinated axons. Bar = 20 μm.

had thin myelin sheaths, often surrounded either by actively phagocytic Schwann cells or macrophages (fig. 3A). These cells additionally or separately contained variable numbers of longitudinally or concentrically arranged lamellae (zebra bodies) within double membrane-bound structures interpreted as secondary lysosomes (fig. 3B). Similar membranous lamellar structures were observed throughout the CNS.

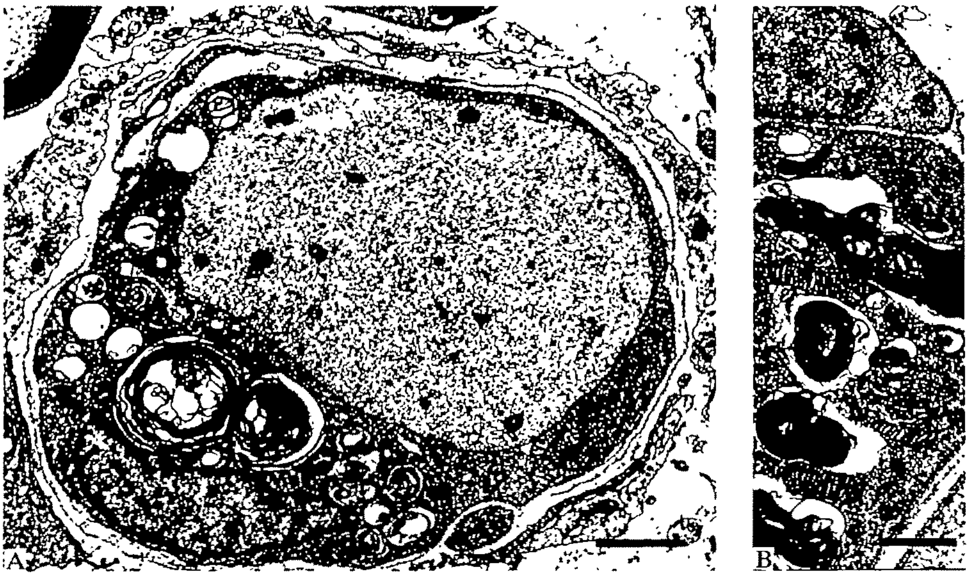

FIG. 3. A, electron micrograph of a demyelinated axon surrounded by a Schwann cell containing myelin debris. Bar = 2 μm. B, electron micrograph illustrating characteristic membrane-bound lamellar inclusions within cytoplasm of a Schwann cell. Bar = 1 μm.

Biochemical analysis

Lysosomal enzyme analysis (Table 2). There was a severe reduction in sphingomyelinase activity (pH 5.0) to 5% of normal and a 50% decrease in ceramidase activity in the brain of Cat 1, compared with the age-matched control. The other brain lysosomal enzymes were within the expected range for normal cats. Splenic lysosomal enzyme analysis performed in Cat 3 also demonstrated a marked deficit in sphingomyelinase activity, where levels of 10% of normal were measured. These results are comparable with Niemann-Pick disease type A with sphingomyelinase activity at levels of 0–5% of normal (Wenger, 1977; Wenger *et al.*, 1980; Brady, 1983; Kudoh *et al.*, 1983).

TABLE 2. LYSOSOMAL ENZYME ANALYSIS*

	Brain		*Spleen*	
	Cat 1	*Control*	*Cat 3*	*Control*
Sphingomyelinase	0.8[a]	15.5[a]	0.1[b]	1[b]
Ceramidase	0.36[a]	0.72[a]	–	–
Hexosaminidase	170	187	930	480
Glucocerebrosidase	–	–	26[b]	9.8[b]
Arylsulfatase A	23.6	14.4	–	–
Arylsulfatase B	26.9	39.9	–	–
Arylsulfatase C	50.5	43.9	–	–
α-galactosidase	50.8	32.9	–	–
β-galactosidase	42.9	52.0	–	–
α-iduronidase	5.2	3.9	–	–

* In nmol/mg protein/h. [a] Mean of 2 readings. [b] Mean of 3 readings.

Lipid fractionation. Following lipid fractionation with silicic acid columns, semi-quantitation of the sphingomyelin component of fraction IV (phospholipid fraction) (Table 3) demonstrated a 3½-fold increase in this substrate in both the liver and kidney cortex of Cat 1 when compared with the age-matched control.

Analysis of splenic lipid extracts in Cat 3 showed a striking 25-fold accumulation of sphingomyelin and a substantial 6-fold increase in unesterified cholesterol (Table 4). In addition, a phospholipid which was present at undetectably low levels in normal spleen was a prominent component of the phospholipid pool in the affected spleen. This lipid was identified as bis(monoacylglyceryl) phosphate (BMAGP) by its TLC separation from cardiolipin in solvent system D (bis(monoacylglyceryl) phosphate and cardiolipin

TABLE 3. SEMIQUANTITATIVE ANALYSIS OF SPHINGOMYELIN (CAT 1)

	Liver		*Kidney*	
	Cat 1	*Control*	*Cat 1*	*Control*
Sphingomyelin (mg/g formalin wt)	35	10	30	8

TABLE 4. QUANTITATION OF LIPID (LOWER PHASE) FRACTIONS (CAT 3)

	Brain		*Spleen*	
Lipid (mg/g wet wt)	*Cat 3*	*Control*	*Cat 3*	*Control*
Sphingomyelin	28	4.1	69 ± 12	2.6 ± 0.7
Free cholesterol	21	13	16 ± 1.4	2.7 ± 0.3
Phosphatidyl choline	12	15	7.2	2.9
Phosphatidyl ethanolamine	22	12	6	3.3
Phosphatidyl serine	7.5	5.2	2.3	1.5
Bis(monoacylglyceryl) phosphate	–	–	2.8[a]	ND[b]
Free fatty acid	0.56	0.53	1.1	0.55
Cholesterol fatty ester	–	–	1.3	0.14
Triglycerides	–	–	3.9	0.18

[a] Bis(monoacylglyceryl) phosphate measured relative to phosphatidyl ethanolamine standards. [b] ND = not detected.

comigrate in solvent systems A and B). The elevation of sphingomyelin and BMAGP in the splenic phospholipids of this affected cat can be readily seen by two-dimensional TLC (fig. 4).

Assessment of fraction IV of the whole lipid lower phase of the brain of Cat 1 compared with the control indicated only a modest increase in sphingomyelin content, whereas

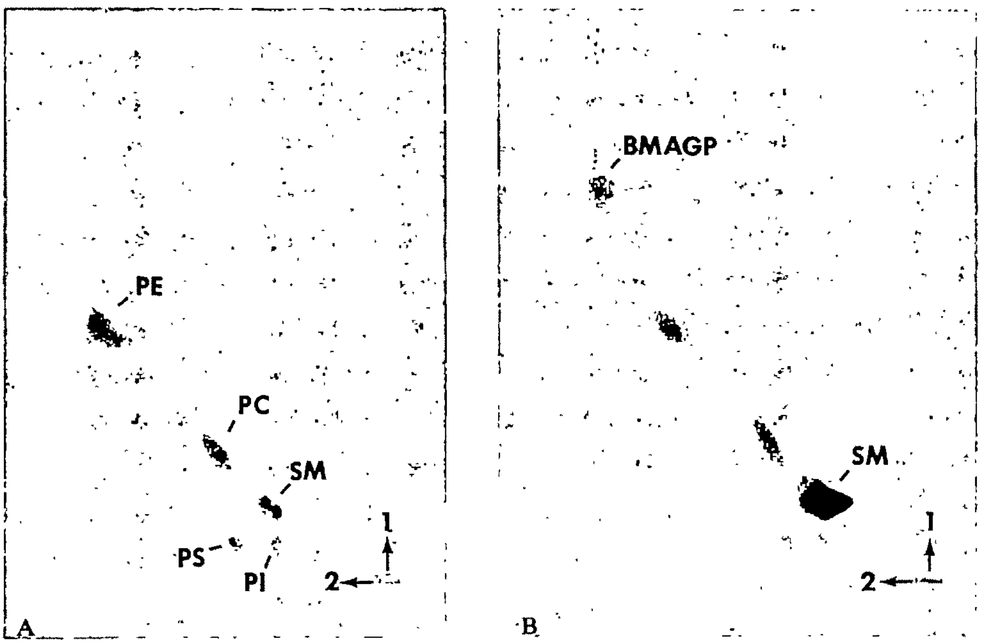

FIG. 4. Two-dimensional TLC of splenic phospholipids. A, lower phase lipid extract from 4.6 mg (wet wt) of splenic tissue from a normal control. B, lower phase lipid extract from 2.3 mg (wet wt) of splenic tissue from Cat 3. Solvent systems: 1 = chloroform:methanol:29% aqueous NH_3 (65:35:5); 2 = chloroform:acetone:methanol:acetic acid:water (20:8:4:4:2). PI = phosphatidyl inositol; PS = phosphatidyl serine; PC = phosphatidyl choline; PE = phosphatidyl ethanolamine; SM = sphingomyelin; BMAGP = bis(monoacylglyceryl) phosphate.

in Cat 3, a 7-fold accumulation of sphingomyelin and a mild increase in free cholesterol to 160% of normal were observed (Table 4).

Thin layer chromatography of the major ganglioside fraction (upper phase) in the brains of both Cats 1 and 3 did show a generalized increase in total brain gangliosides compared with controls, with qualitative increases in the GM_2 and GM_3 bands. Quantitation of the brain ganglioside profile observed in Cat 3 demonstrated that both GM_2 and GM_3 were disproportionately increased by 10-fold over their values in normal brain without significant alterations in any of the other measured gangliosides (Table 5). These changes in brain gangliosides in Cat 3 parallel those observed for a Balinese cat model of type A Niemann-Pick disease (Baker *et al.*, 1987).

TABLE 5. QUANTITATION OF BRAIN GANGLIOSIDE (UPPER PHASE) FRACTION (CAT 3)

	% distribution of sialic acid in gangliosides	
Ganglioside species	*Cat 3*	*Control*
GM_4	2.9	3.2
GM_3	11.1	0.96
GM_2	13.0	1.1
GM_1	19.0	19.0
GD_{1a}	18.0	38.0
GD_{1b}	11.0	12.0
GT_{1b}	13.0	13.0
Unidentified	12.0	13.0

Sphingomyelinase activity in cultured skin fibroblasts

The average sphingomyelinase activity in cultured skin fibroblasts (from 2 duplicate measurements), calculated for each of 8 cats related to Cats 1 and 2, is presented in Table 6. There was no significant decrease in sphingomyelinase activity in any of the 6 inbred cats, compared with the means of the 3 human controls and 2 cats produced by outcross matings.

TABLE 6. ^{14}C-SPHINGOMYELINASE ACTIVITY IN CULTURED SKIN FIBROBLASTS OF RELATED CATS

Mean sphingomyelinase activity (nmol/mg protein/h)										
Cat A[a]	*Cat B*[b]	*Cat C*[c]	*Cat D*	*Cat E*	*Cat F*	*Cat G*[d]	*Cat H*[d]	*Human control 1*	*Human control 2*	*Lab. human control Mean ± 2 SD*
103.5	126	80	149.5	85.5	112	101.5	98.5	149.5	93	75 ± 38

[a] Cat A = Father of Cat 1; [b] Cat B = Grandmother of Cat 1; [c] Cat C = Full sister of sire of Cat 2; [d] Cat G & H = 2 outcross matings.

DISCUSSION

We have demonstrated that feline Niemann-Pick disease, despite generalized nervous system involvement, can present as a primary demyelinating polyneuropathy, a previously undescribed syndrome. The severe peripheral nerve involvement was demonstrated by electrophysiology, histochemistry and light and electron microscopy. Lysosomal enzyme analysis and sphingomyelin semiquantitation confirmed the diagnosis of Niemann-Pick disease, although a deficit of sphingomyelinase could not be demonstrated in cultured fibroblasts from cats related to Cats 1 and 2, including at least 1 known heterozygote.

Based on the severe slowing of both motor and sensory nerve conduction velocities, the polyphasia and the temporal dispersion seen in all the recorded action potentials on electrophysiology, a diagnosis of a primary demyelinating polyneuropathy was made. The mild electromyographic changes and variable reduction in motor and sensory evoked action potential amplitudes suggested mild axonal involvement, although this was not supported by muscle histochemistry and peripheral nerve pathology.

Light microscopy revealed dramatic changes in dorsal root ganglion cells, and myelinated fibres in cranial nerves, nerve roots and all peripheral nerves. These changes ranged from the presence of metachromatic granules and vacuolar material in ganglion cells to partial or complete demyelination and remyelination of the majority of axons in the latter two regions. In the endoneurium, macrophages contained significant quantities of myelin debris and metachromatic granules. On electron microscopy these cells, as well as Schwann cells, contained large numbers of secondary lysosomes within their cytoplasm, incorporating lamellar structures in variable orientations. These changes are very similar to the peripheral nerve pathology observed in the 2 isolated human cases of polyneuropathy in type A Niemann-Pick disease (Gumbinas *et al.*, 1975; Landrieu and Saïd, 1984). Further detailed light and electron microscopic studies of the CNS and PNS, and morphometry and teased nerve fibre analysis of the peripheral nerves in feline Niemann-Pick disease polyneuropathy are in preparation.

The documented cases of Niemann-Pick disease in the cat have been reported to be type A, with classic, early onset neurological involvement, and a profound deficiency of acid sphingomyelinase, an increase in tissue sphingomyelin and cholesterol and a selective increase in brain GM_2 and GM_3 gangliosides (Percy and Jortner, 1971; Wenger *et al.*, 1980). By these criteria, the third cat in this study appears to represent the classic type A phenotype of Niemann-Pick disease. In addition, Cat 3 displayed a marked elevation of bis(monoacylglyceryl) phosphate in the splenic phospholipid pool. This lysosomal phospholipid is elevated in all variants of Niemann-Pick disease in man (Rao and Spence, 1977; Vanier, 1983; Huterer and Wherrett, 1985) and was detected in a mouse model of type C Niemann-Pick disease (Pentchev *et al.*, 1980). This specific phospholipid is uniquely synthesized and localized in lysosomes, suggesting that its elevation reflects a proliferation of secondary lysosomes due to the accumulation of intracellular material (Pentchev *et al.*, 1980).

By contrast, even though the tested feline homozygote (Cat 1) did show a 10 to 20-fold decrease in sphingomyelinase activity and a qualitative increase in brain gangliosides, as would be expected in type A Niemann-Pick disease, there were biochemical findings seen in this cat, and in cats related to Cats 1 and 2, which are at variance with this syndrome. (1) There was only a 3 to 4-fold increase in sphingomyelin content in the liver and kidney compared with the normal controls, which is not as marked as in the tissues of the reported classic human and feline type A patients, including Cat 3 (sphingomyelin content being 5 to 50× normal) (Wenger, 1977; Wenger *et al.*, 1980; Brady, 1983; Baker *et al.*, 1987). (2) There was only a modest increase in brain sphingomyelin content. However, human type A patients often have significantly less sphingomyelin storage in the brain compared with other tissues, with occasional reports of normal values (Wenger, 1977). The third cat, biochemically representing classic Niemann-Pick disease type A, did show a 7-fold increase in brain sphingomyelin over control values. (3) There was no significant difference in fibroblast sphingomyelinase activity between related cats (including 1 known heterozygote) and cats produced by outcross matings and human controls. This is not consistent with the 50% reduction in sphingomyelinase levels in human type A heterozygotes (Jungalwala and Milunsky, 1978; Wenger *et al.*, 1980; Brady, 1983). The lack of detectable enzyme deficiency in known heterozygotes and the modest accumulation of sphingomyelin in the homozygote liver and kidney are more consistent with type C Niemann-Pick disease, although the almost nondetectable brain sphingomyelinase activity seen in these affected cats points strongly against this association (Wenger, 1977; Pentchev *et al.*, 1980; Brady, 1983). Type C Niemann-Pick disease classically shows only a partial deficiency (40%) to normal levels of acid sphingomyelinase and it has been suggested that the deficiency of sphingomyelinase is not the primary defect in this type C variant (Wenger, 1977; Brady, 1983; Elleder *et al.*, 1985; Levade *et al.*, 1985). This therefore suggests that the 2 related cats represent a variant of classic type A Niemann-Pick disease. In man, it has been reported that significant variability can exist in the biochemical abnormalities in type A patients (Wenger, 1977).

One possible explanation for the normal sphingomyelinase activity in the suspected heterozygote cats could be that this disease manifestation represents a spontaneous mutation. However, this is unlikely since 2 closely related kittens developed the same rare storage disease at the same time. In addition, the validity of the testing procedure may also be questioned. All samples, however, were tested in duplicate and the accuracy of testing for heterozygotes of Niemann-Pick disease type A using fibroblast cultures is well established in man (Callahan and Khalil, 1975; Wenger, 1977; Vanier *et al.*, 1980; Brady, 1983). It is considered more reliable than leucocyte assays where some overlap with the normal population occurs (Vanier *et al.*, 1980). Further testing to clarify this Niemann-Pick disease variant in future animals would include brain lipid histochemistry (Elleder *et al.*, 1985), the ability of cultured fibroblasts to esterify exogenously derived cholesterol (Pentchev *et al.*, 1985) and isoelectric focusing of isoenzymes (Callahan and Khalil, 1975; Wenger, 1977).

The 50% reduction of ceramidase activity in Cat 1 compared with control values may be secondary to a decrease in appropriate substrate. Due to the primary defect in sphingomyelinase activity, ceramide, one of the two cleavage products produced by the action of this enzyme on sphingomyelin will be substantially reduced. Although ceramide is one of the end products of other metabolic pathways (e.g., globoside catabolism), its lack of production in the sphingolipid pathway may result secondarily in a decreased requirement for ceramidase in nervous tissue. Furthermore, there was a secondary increase in hexosaminidase and glucocerebrosidase in the spleen of Cat 3 compared with control values. This is not an uncommon phenomenon in lysosomal storage diseases and may represent either an attempt to compensate for the deficient enzyme by a general increase in lysosomal activity, or lysosomal disruption and enzyme extrusion caused by the accumulating lipid within the lysosomes (Brady *et al.*, 1970). This is not a consistent finding, however, and probably has no diagnostic or comparative significance.

Polyneuropathy associated with feline Niemann-Pick disease is the first described inherited primary polyneuropathy in the cat and may add valuable future insight into this sparsely documented manifestation of this lysosomal storage disease in man. The presenting peripheral nerve disease in these 3 cats is at variance with the cerebral/cerebellar signs reported in previous feline cases and therefore demonstrates the potential variability of clinical signs of Niemann-Pick disease in this species. Despite very similar clinical and pathological abnormalities between these 3 cats, certain biochemical features in the first 2 related cats were at variance with the 'classic' Niemann-Pick disease type A enzyme and lipid analysis observed in Cat 3. This stresses the fact that biochemical varability can also exist in feline Niemann-Pick disease, as it does in man.

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MULTIPLE SCLEROSIS AMONGST CHINESE IN HONG KONG

by Y. L. YU,[1] E. WOO,[1] B. R. HAWKINS,[2] H. C. HO[2] *and* C. Y. HUANG[1]

(*From the Departments of Medicine*[1] *and Pathology,*[2] *University of Hong Kong*)

SUMMARY

A territory-wide investigation of southern Chinese patients with multiple sclerosis (MS) was conducted in Hong Kong. There were 47 patients, 35 of whom were clinically definite (CDMS), 6 laboratory-supported definite (LSDMS) and 6 clinically probable (CPMS). The prevalence rate was 0.88 per 10^5 population, which is of the same order as in other Oriental populations but much lower than in Caucasoid populations. Comparisons with major Oriental and Caucasian series showed essentially the same clinical picture with only minor variations. In one autopsy case, the lesions were found mainly in the optic nerves and spinal cord, with marked softening in addition to the classical demyelination features. In contrast to findings in Caucasians, the detection rate of oligoclonal bands in the cerebrospinal fluid was low (33% in CDMS patients) and there was no association with human leucocyte antigens. The possible implications of these findings on the pathogenesis of MS are discussed.

INTRODUCTION

Multiple sclerosis (MS) is an acute, subacute or chronic disorder of the central nervous system, often beginning in early adult life, which pursues a remittant, irregular or prolonged course with widely distributed lesions. Clinical and pathological descriptions published by Cruveilhier (1835–1842) and Carswell (1838) are generally regarded as the earliest systematic accounts. The other notable historical landmark was the comprehensive investigation by Charcot (1868), who referred to the disease as 'la sclérose en plaques disseminées' and proposed the diagnostic criteria known as Charcot's triad: intention tremor, scanning speech and nystagmus. Because of its relatively high prevalence in Caucasians, the elusive nature of its aetiology and pathogenesis, the lack of effective treatment so far, and its socioeconomic implications, MS has been one of the most extensively studied and reported neurological disorders in Caucasians.

In contrast, largely because of its low prevalence in Orientals, MS has been reported only infrequently (Kuroiwa *et al.*, 1977). The Japanese are by far the best studied of the non-Caucasoid populations, with accurately documented prevalence and clinical data available (Okinaka *et al.*, 1958, 1960; Kuroiwa and Shibasaki, 1973; Shibasaki and Kuroiwa, 1973; Kuroiwa *et al.*, 1975, 1983; Shibasaki *et al.*, 1981). Reports from other Oriental populations include Koreans (Pernov, 1957; Oh, 1962; Park, 1960, 1966; Kurtzke *et al.*, 1968), Thais (Vejjajiva, 1973), and Indians (Mathew *et al.*, 1971; Dastur and Singhal, 1973; Singhal and Wadia, 1975). In Chinese, Woods (1929) alluded to

Correspondence to: Dr Y. L. Yu, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong.

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2 cases of MS in his review of neurological disorders. From Taiwan, Hung *et al.* (1976) described 25 patients, including 4 who were reported by Hung and Lin in 1956; autopsy confirmation was available in 2 patients. From Mainland China, Liu *et al.* (1958) reported 5 cases in 1958. Subsequently Zhao *et al.* (1979) delineated the clinical picture of MS in 70 northern Chinese, and Guo (1979) described the details of autopsy findings in 2 patients of this series. Zhao and Liu (1979) presented the clinical features of 25 cases from the southern Chinese Province of Guangdong, of whom 3 had autopsy data.

Hong Kong is located to the south of Guangdong Province of Mainland China (latitude 22°20′N, longitude 114°12′E), and has a predominantly Chinese population of 5.65 million (Census and Statistics Department, Hong Kong Government, 1987). The medical service is comprehensive and available to all citizens. In the past 7 years, the neurology specialty has expanded rapidly in terms of trained neurologists and modern investigative facilities. Multiple sclerosis has been increasingly diagnosed during this period. It was in this context that a territory-wide investigation of MS was undertaken in order to determine the prevalence, clinical picture and human leucocyte antigen (HLA) profile.

PATIENTS AND METHODS

Between January 1, 1981 and December 31, 1987, a territory-wide study of MS was carried out in Chinese patients in Hong Kong. All neurologists, neurosurgeons and physicians in institutions or private practice were asked to refer their patients with definite or suspected MS for documentation and investigation. Patients who were alive at any point in this period were included.

In all patients, a detailed history was obtained including demography, place of birth, age of migration to Hong Kong, family history, history of measles infection in childhood, viral infections and events preceding the onset of symptoms, pattern of progress and duration of the illness, and the response to treatment. A full neurological examination was performed at presentation and during regular follow-up visits to determine the sites of lesions as well as the clinical course. The clinical course was classified according to progression. In the nonprogressive form, the functional status was relatively stable and exacerbations were relatively mild, with the disability ranging from nil/mild (NP1) to moderate/severe (NP2). In the progressive form, deterioration was stepwise (P1) or relentless (P2); in either case, the disability was moderate to severe and the disease may have been the underlying cause of death. Disability was assessed according to the disability scale of Kurtzke (1961, 1965) based on mobility, visual impairment, ability to maintain a job, and to maintain bladder and sexual function. Grades 1 and 2 were equivalent to mild disability, 3 to 6 moderate, 7 to 9 severe, and grade 10 indicated death.

A full set of laboratory investigations was performed whenever possible to aid the diagnosis of multiple sclerosis, and to exclude other disorders, in particular connective tissue disease which is common in Hong Kong. Blood tests comprised blood counts, ESR, biochemistry, antinuclear factor, rheumatoid factor, complement factors (C3, C4), and VDRL. Blood and CSF were tested for viral titres against measles, mumps, influenza A and B, echovirus, coxsackie B, rubella, herpes simplex, HTLV I. CSF analyses included cell counts, biochemistry, VDRL, immunoglobulins and oligoclonal IgG bands with paired serum (by Department of Neurochemistry, The National Hospital for Nervous Diseases, Queen Square, London). Other tests included computed tomographic (CT) brain scan (plain and contrast), visual (VEPs), brain stem auditory (BAEPs) and somatosensory (SSEPs) evoked potentials.

Typing for HLA-A, -B and -DR antigens was performed in 40 patients and 100 normal healthy southern Chinese controls recruited from hospital staff, university staff and students. The standard lymphocyte microcytotoxicity test was used, with 'Oriental' ABC and DR typing trays purchased from One Lambda, Inc., California. These trays were supplemented by antisera obtained from local donors or from laboratories overseas. HLA antigen frequencies in patients and controls were compared using a 2×2 contingency analysis (χ^2 test) incorporating Yates' correction for each antigen.

The diagnostic criteria for MS were those of Poser *et al.* (1983). Patients were classified into the following categories: clinically definite (CDMS), laboratory-supported definite (LSDMS), clinically probable (CPMS), and laboratory-supported probable (LSPMS). According to these diagnostic criteria, the laboratory support required for LSDMS and LSPMS is the demonstration in CSF of IgG oligoclonal bands or of increased CNS synthesis of IgG (an elevated IgG/total protein ratio $>12\%$). Devic's disease (neuromyelitis optica) was considered as a syndrome of acute spino-optic demyelination, of which MS is one of the causes, and was defined as bilateral visual impairment and a transverse spinal cord lesion which developed either concomitantly or within several weeks of each other, with or without subsequent improvement (Shibasaki *et al.*, 1974, 1981).

The characteristics of MS patients in this series were compared with major Oriental and Caucasian series (McAlpine *et al.*, 1972; Kuroiwa *et al.*, 1975, 1977; Hung *et al.*, 1976; Poser *et al.*, 1979; Zhao and Liu, 1979; Zhao *et al.*, 1979; Shibasaki *et al.*, 1981), the uniformity of diagnostic criteria and of interpretation of symptomatology being ensured as far as possible.

RESULTS

Prevalence

Forty-seven patients in 3 categories (35 CDMS, 6 LSDMS, 6 CPMS) of MS were entered (Table 1). The population studies was 4.90 million, covering the whole territory except the New Territory East Region with 0.75 million population (Lands and Works Department, Hong Kong Government, 1987). At the prevalence date on December 31, 1987, 4 patients had died. The prevalence rate was therefore 43 in 4.9 million or 0.88 per 10^5 population.

Demography and familial occurrence

All patients were southern Chinese originating in Guangdong province, with the exception of 1 LSDMS patient who was born in Hong Kong but who originated from the northern province of Shantung. There were no instances of familial occurrence.

Clinical picture

Sex ratio and age of onset (Table 1). There were 9 male and 26 female patients with

TABLE 1. SEX DISTRIBUTION AND AGE AT ONSET IN DIFFERENT CATEGORIES OF MS PATIENTS

Age at onset (yrs)	*CDMS*		*LSDMS*		*CPMS*		*Combined*	
	M	*F*	*M*	*F*	*M*	*F*	*M*	*F*
11–20	2	7	2	0	0	0	4	7
21–30	7	8	0	3	2	0	9	11
31–40	0	4	0	1	3	0	3	5
41–50	0	4	0	0	1	0	1	4
51–60	0	3	0	0	0	0	0	3
Mean (SD) (yrs)	30 (13)		23 (8)		23 (10)		29 (12)	
Range (yrs)	13–59		14–25		22–49		13–59	

CDMS = clinically definite MS; LSDMS = laboratory supported definite MS; CPMS = clinically probably MS; M = male; F = female.

CDMS (ratio 1:2.9) and 17 male and 30 female patients (ratio 1:1.8) when the three disease categories were combined. Hence there was a female preponderance. The mean age of onset was 30 yrs in the CDMS patients and 29 yrs in the Combined group.

Mode of onset (Table 2). The time for evolution of symptoms to the maximum degree was 1 wk for acute onset, 1 month for subacute onset and more than 1 month for insidious onset. Over 90% of patients had either an acute or subacute onset.

Preceding events at onset and relapse. Preceding events were defined as events occurring 2 wks before onset. These were not present in most patients either at onset (65.6%) nor at relapse (86.4%). Viral infections presenting as fever, upper respiratory tract infection or gastroenteritis were the commonest antecedent events. The other events included pregnancy, physical exertion, mental stress and minor medical procedures.

Initial neurological symptom(s) (Table 3). In the CDMS group, the commonest presentation was visual loss (37%), followed by spinal cord dysfunction, diplopia and ataxia. In the Combined patients group, spinal cord dysfunction was more common than visual impairment.

Clinical features during the course of disease (Table 4). The frequency with which symptoms and signs were detected was similar in the CDMS and Combined patient groups. Spinal cord symptomatology ranked first, manifesting commonly as paraparesis, tetraparesis, sensory level and sphincter disturbance. Lhermitte's sign which reflects a cervical cord lesion of some severity, was elicited in about one-fifth of all patients. Paroxysmal disturbance in 6 CDMS patients caused them considerable distress, but was controlled effectively by carbamazepine. The symptoms consisted of severe attacks of pain and dysaesthesiae affecting either the upper or lower limbs, and in 2 patients these were followed by cramps in the affected limb(s). The attacks were not accompanied by disturbance of consciousness, articulation or facial sensation. All 6 patients had definite and/or marked spinal cord dysfunction, and only 2 had mild additional brainstem-cerebellar features.

Visual loss occurred in 69% of the CDMS patients and in 57% of the Combined patients group. Optic atrophy was detected in about two-thirds. Bilateral involvement, either simultaneous or consecutive, was more common than unilateral (ratio 2.8 to 1 in the CDMS and 1.8 to 1 in the Combined patients group). Total or near total bilateral blindness was present in 5 CDMS patients (14%). Cerebellar ataxia occurred in about half of the CDMS and Combined patients, some of whom also had nystagmus and/or vertigo and dizziness. Diplopia was encountered in about one-quarter, with ocular palsy due to sixth nerve palsy being the commonest lesion. Internuclear ophthalmoplegia was present in 4 CDMS and 1 LSDMS patients. Other brainstem signs included ptosis, facial sensory disturbance, facial nerve palsy and bulbar palsy. Cerebral symptoms, mainly in the form of mental changes such as impaired cognition, depression and euphoria, and less often as epileptic seizures, occurred in about one-third of patients.

Site of clinical lesions (Table 5). In the CDMS patients, the spinal cord was the site most frequently involved, followed by the optic nerves, brainstem-cerebellum and cerebral hemispheres. In the Combined patients group, the spinal cord and the brainstem-cerebellum were affected with equal frequency.

TABLE 2. NATURAL HISTORY OF THE PRESENT SERIES OF MS IN COMPARISON WITH OTHER REPORTED SERIES

	Hong Kong		*Taiwan*	*Beijing*	*Guangdong*	*Asia*	*Japan*	*Kyushu/London*		*England*	*Germany*
	CDMS	*Combined*	(*Hung et al.*, 1976)	(Zhao *et al.*, 1979)	(Zhao and Liu, 1979)	(Kuroiwa *et al.*, 1977)	(Kuroiwa *et al.*, 1975)	(Shibasaki *et al.*, 1981)		(McAlpine *et al.*, 1972)	(Poser *et al.*, 1979)
	(35)	(47)*	(25)	(70)*	(25)*	(61)*	(1084)*	(60)	(204)	(282)*	(1271)*
Male:female ratio	1:2.9	1:1.8	1:1.4	1:1.8	1:2.1	1:1.9	1:1.3	1:1.5	1:2.0	1:1.6	1:1.5
Age at onset: mean (SD) (yrs)	30 (13)	29 (12)	32 (14)	31	range 15–24	29	33	31 (10)	31 (9)		31
Onset (%)											
Acute	49	51	64	0		57	47	75	79	68	
Subacute	43	40	28	90							
Chronic	8	9	8	10							
Familial occurrence (%)	0	0	0	1.4	0		2	0	10	6.5	6.5
Clinical course (%)											
NP1 and NP2	74	77	36	90	72	85	74	85	64		31
P1	9	6	64					10	31		50
P2	17	17	0					2	5		
Neuromyelitis optica (%)	5.7	4.2	8			7	8	3	0		

No. of patients in parenthesis; * includes categories other than CDMS, blank = data not available. NP1 = nonprogressive form 1; NP2 = nonprogressive form 2; P1 = progressive form 1; P2 = progressive form 2 (*see* text for explanation)

TABLE 3. INITIAL SYMPTOM(S) (PERCENTAGE OF PATIENTS)

	Hong Kong										
Initial symptom	*CDMS* *(35)*	*Combined* *(47)**	*Taiwan* *(25)*	*Beijing* *(70)**	*Guangdong* *(25)**	*Asia* *(61)**	*Japan* *(1084)**	*Kyushu* *(60)*	*London* *(204)*	*England* *(282)**	*Germany* *(1271)**
Visual loss	37	31	56	30	16	43	45	48	25	24	36
Unilateral	17	15		19		28		27	21		
Bilateral	20	16		11		21		22	3		
Sensory disturbance	34	37	32	31	20	31	28	35	35	47	41
Face	8	9									
Limb/trunk	26	28									
Weakness/stiffness	31	33	40	26	44	39	23	27	19	50	43
Sphincter dysfunction	17	22	4	2				7	5		10
Diplopia	23	20	4	3	4	15	11	8	11		13
Ptosis	3	2			8						
Facial palsy	3	2	4	3				3	0		7
Ataxia	6	11		6		10	25	12	18	14	
Dizziness/vertigo	3	2						0	3		
Nausea/vomiting	3	2			8						
Mental change	0	2			4						
Speech disturbance	0	2		3	4	8	8	5	3		

No. of patients in parentheses; * includes categories other than CDMS; blank = data not available.

TABLE 4. NEUROLOGICAL SYMPTOMS AND SIGNS DURING THE COURSE OF DISEASE (PERCENTAGE OF PATIENTS)

	Hong Kong									
Symptoms and signs	*CDMS* (35)	*Combined* (47)*	*Taiwan* (25)	*Beijing* (70)*	*Guangdong* (25)*	*Asia* (61)*	*Japan* (1084)*	*Kyushu* (60)	*London* (204)	*Germany* (1271)*
Mental change	29	26	20			19	26	15	22	39
Lethargy, imparied consciousness				26	52			20	5	
Convulsion	9	6						5	2	
Visual loss	69	57	92	69	68	70	81	80	73	66
Unilateral	18	17	36	16			17	15	23	
Bilateral	51	30	56	53			64	65	50	
Optic atrophy	46	37		57	36		64	70	71	
Unilateral	15	13					18	18	20	
Bilateral	31	24					46	52	51	
Diplopia	28	24	20	23	44			35	39	34
Ptosis	6	5								
Ocular palsy	23	22		23	44			28	16	
Internuclear ophthalmoplegia	11	11	8					18	24	
Nystagmus	14	17	32	27	36			50	56	
Facial sensory disturbance	14	17	4	19	24			17	12	
VIII n. palsy	6	6	16	9				20	10	23 (incl. Vn.)
Hearing loss/tinnitus	0	0	16	7	12			8	8	
Vertigo/dizziness	9	9	12					12	17	
Dysarthria	14	15	36			26	39	47	31	
Dysphagia	3	2	32	20	40		21	23	3	
Ataxia	55	48	24	31	44	30	51	58	84	82
Nausea, vomiting	9	7								
Motor weakness	83	78		87	84		79	80	80	88
Paraparesis	51	46		44				30	30	
Quadriparesis	37	29	96	31	36			27	9	
Hemiparesis	9	13	4	11				33	10	
Monoparesis	0	0						22	9	
Respiratory distress	6	5		3						
Hyperreflexia	71	70	92	68	80			92	87	
Babinski reflex	69	65	88	86				67	84	
Muscle atrophy	0	0	12					8	6	
Paroxysmal pain and/or spasm	17	13	28	17	12	23	12	28	4	
Paraesthesiae	69	66	44					77	84	
Pain	17	11						35	37	
Girdle sensation	23	23						27	9	
Sensory signs	83	74			64		77	27	9	87
Lhermitte's	23	17	28	3		16		42	15	
Sensory level	57	50		67				43	26	
Segmental loss	9	7	76	21				32	8	
Hemisensory loss	11	13		9				22	9	
Sphincter dysfunction	63	59	96		48	52	47	58	74	63

No. of patients in parentheses; * includes categories other than CDMS; blank = data not available.

TABLE 5. SITES OF CLINICAL LESIONS (PERCENTAGE OF PATIENTS)

	Hong Kong						
	CDMS (35)	*Combined (47)**	*Beijing (70)**	*Asia (61)**	*Japan (1084)**	*Kyushu (60)*	*London (204)*
Optic nerve	70	60	69	80	82	80	85
Spinal cord	82	69	83	78	82	68	76
Brainstem-cerebellum	67	69	40	35	63	71	70
Cerebrum	27	26	29	18	40	40	27

No. of patients in parenthesis; * includes categories other than CDMS; blank = data not available.

TABLE 6. DISABILITY AT LAST EXAMINATION (PERCENTAGE OF PATIENTS)

	Hong Kong							
Kurtzke scale	*CDMS (35)*	*Combined (47)**	*Taiwan (25)*	*Beijing (70)**	*Asia (61)**	*Japan (1084)**	*Kyushu (60)*	*London (204)*
0 (nil)	9	17	0	25	23	18	25	10
1–2 (mild)	39	36	32		33	27	27	26
3–6 (moderate)	21	23	28	36	27	37	33	38
7–9 (severe)	20	15	12	26	17	18	15	26
10 (dead)	11	9	29	13			6.7**	1.5**

No. of patients in parenthesis; * includes categories other than CDMS; ** this figure is a percentage of the patient population, calculated separately from the disability data; blank = data not available.

Clinical course and disability (Tables 2, 6). The mean follow-up periods for CDMS and Combined patients were 73.6 months (SD 48.4) and 66.3 months (SD 46.4), respectively. In both the CDMS and Combined patients groups, the nonprogressive form of disease was found in about three-quarters. The milder variety NP1 was predominant: 73% in CDMS, 80% in LSDMS and 100% in CPMS. Of the 11 patients with progressive disease, stepwise deterioration (P1) occurred in 3 CDMS patients, and relentless deterioration (P2) in 6 CDMS, 1 LSDMS and 1 CPMS patients. The disability at last examination mirrored the clinical course. In about half, the disability was grade 0 to 2 (nil and mild) and in about one-third, the grades were 7–10 (severe or dead), with CDMS patients more disabled in general. Even though CDMS patients had a greater proportion of disability disease than LSDMS and CPMS patients, 69% led an independent life and over 40% of them could maintain their jobs. The mean intervals between onset and last relapse were 51.6, 18.5 and 15.8 months in CDMS, LSDMS and CPMS respectively. In the CDMS group, there were 2.5 relapses on the average, with 71% patients having 1 or 2 relapses, 20% having 3 to 5 relapses and the remaining 9% having 6 to 10 relapses. The relapse rate was 0.44 per year. In the LSDMS and CPMS groups, most patients had a single attack and only 2 patients in each group had a single relapse.

CT brain scans

Of the 27 CDMS patients on whom CT was performed, low attentuation in the periventricular white matter was present in 12. There was agreement of CT and clinical findings in 20 patients; CT detected subclinical cerebral lesions in 5 patients, but showed no abnormality in 2 patients with cerebral symptoms. One of 6 LSDMS patients had WMLA while all other LSDMS and CPMS patients had normal CT, the CT-clinical correlation being good in these 2 groups.

Findings in cerebrospinal fluid (Table 7)

Pleocytosis was seen in 73% of all patients, the majority of whom had white cell counts less than 50/μl. There were no patients with cell count above 100/μl. Lymphocytic predominance was the rule. Protein concentration was normal (<0.45 g/l) in 60% of patients and was only mildly elevated (<1 g/l) in the remainder. For both the CDMS and Combined patient groups, the absolute IgG level was elevated (>0.055 g/l) in about one-third, whereas the IgG/protein ratio was elevated ($>12\%$) in about one-half. Oligoclonal bands were present in only 33% of CDMS patients in samples obtained during an active phase of the disease. The CSF of these patients was not reexamined during the inactive phase of disease. However, oligoclonal bands were absent in 28% of CDMS patients whose disease was active at the time of examination. Five of the 6 patients with LSDMS in whom the IgG/total protein ratio was examined had elevated ratios. Three patients with LSDMS were examined for oligoclonal bands, of whom 2 were positive; in these 2 patients the CSF was sampled during the active stage of the

TABLE 7. CSF FINDINGS (PERCENTAGE OF PATIENTS)

	CDMS	*LSDMS*	*CPMS*
[1]WBC/μl			
0	21	67	17
<10	52	33	49
10–49	21	0	17
50–100	6	0	17
[1]Lymphocytes (%)			
61–80	8	0	0
81–100	92	100	100
[1]Protein (g/l)			
<0.45	55	83	67
0.45–1.0	45	17	33
[2]IgG (g/l)			
0.025–0.055	67	67	80
>0.055	33	33	20
[2]IgG/protein (%)			
5–12	55	17	100
12.1–30	45	83	0
[3]Oligoclonal IgG			
+ve when examined at			
onset/rel./prog.	33	67	0
remission	0	0	0
−ve when examined at			
onset/rel./prog.	28	0	33
remission	39	33	67

[1] In 33 CDMS, 6 LSDMS and 6 CPMS patients. [2] In 29 CDMS, 6 LSDMS and 5 CPMS patients. [3] In 18 CDMS, 3 LSMS and 3 CPMS patients; prog. = progressive; rel. = relapse.

disease, whereas in the patient without oligoclonal bands, the CSF was obtained when the disease was in remission. Oligoclonal bands were absent in all 3 CPMS patients in whom the test was performed, 1 at onset and the others during remission of disease.

HLA profile (Table 8)

The results in 34 patients seen before 1987 have been reported previously (Hawkins *et al.*, 1988). Six further cases have since been studied and the findings do not differ substantially from the earlier results. There was no statistically significant difference between the frequency of any HLA antigen between the patients (either CDMS or

TABLE 8. HLA ANTIGEN FREQUENCIES IN CHINESE PATIENTS WITH MS AND NORMAL CONTROLS

	All MS (*n* = *40*)		*Clinically definite MS* (*n* = *27*)		*Controls* (*n* = *100*)
Antigen	*Obs*	*%*	*Obs*	*%*	*(%)*
HLA-A					
A2	21	52.5	15	55.6	53.0
A3	1	2.5	1	3.7	6.0
A24	11	27.5	8	29.6	22.0
A10	1	2.5	1	3.7	5.0
A11	20	50.0	13	48.1	58.0
A11s	2	5.0	1	3.7	9.0
A30/31	4.	10.0	1	3.7	3.0
A32	1	2.5	1	3.7	0.0
Aw33	10	25.0	9	33.3	25.0
HLA-B					
B51	6	17.5	4	18.5	11.0
Bw52	1	2.5	1	3.7	0.0
B7	1	2.5	1	3.7	2.0
B12	3	7.5	2	7.4	3.0
B13	4	10.0	0	0.0	17.0
B15	11	27.5	7	25.9	35.0
B16	8	20.0	3	11.1	10.0
B17	5	12.5	4	14.8	17.0
Bw22	8	20.0	5	18.4	13.0
B27	0	0.0	0	0.0	5.0
B35	3	7.5	2	7.4	6.0
B37	0	0.0	0	0.0	1.0
B40	13	32.5	10	37.0	29.0
Bw46	8	20.0	8	29.6	31.0
Bw48	5	12.5	4	14.8	5.0
HLA-DR					
DR1	1	2.5	1	3.7	0.0
DR2	20	50.0	12	44.4	38.0
DR3	3	7.5	3	11.1	8.0
DR4	8	20.0	4	14.8	26.0
DR5	10	25.0	8	29.6	14.0
DRw6	5	12.5	5	18.5	25.0
DR7	5	12.5	2	7.4	11.0
DRw8	4	10.0	2	7.4	11.0
DRw9	9	22.5	7	25.9	21.0
DRw10	0	0.0	0	0.0	2.0

Combined patients group) and controls. However, some antigens not commonly seen in southern Chinese were present in these patients. One patient provided the first example of HLA-Bw52 and another the first example of HLA-A32 seen during the testing of over 2,300 southern Chinese in Hong Kong. Four patients (11.8%) possessed antigens having characteristics of A30 and A31 whereas these antigens normally occur in only approximately 3% of southern Chinese. HLA-Bw46, which is a typically southern Chinese antigen, occurred in only 11.8% of the patients compared with 31% of normal controls.

Other investigations

Viral serology, including measles and HTLV1 antibodies, was performed in the CSF and blood in 30 and 34 patients, respectively. In no sample was there a raised titre.

Multimodal evoked potentials studies were performed in 42 patients. The detection rate for clinical and subclinical abnormalities was high: 88% for SSEPs, 86% for VEPs and 74% for BAEPs. The presence of clinical lesions was, however, reflected in 12%, 14% and 26% for SSEPs, VEPs and BAEPs respectively; in some cases this could be attributed to the fact that the study was performed in the remission phase of the disease.

ILLUSTRATIVE CASES

Case 23 (CDMS)

L.S.K., a 42-yr-old housewife, presented in September 1984 with painless visual loss in the left eye developing over 2 days. A week later, her right leg became weak and was paralysed within a few days. She received a short course of corticosteroid treatment at another hospital. There was almost full recovery of her right leg over 3 months, but her left eye blindness remained static. In September 1985, she developed weakness, unsteadiness and paraesthesiae in both legs and arms, followed by urinary and faecal incontinence. Her condition deteriorated and she became bedridden. A 2-wk course of steroids was given. Her recovery was partial but she was able to walk unaided after 2 months. In February 1986, she had another relapse with tetraparesis, a sensory level at C4 segment and incontinence. Steroid treatment was again followed by partial improvement but only of the upper limb function. Three months later, she developed an acute onset of blindness in the right eye which became permanent.

She was transferred to Queen Mary Hospital for further management in September 1986. On examination, higher mental functions were impaired: short-term memory was poor and in the serial 7 test she could not get beyond 93-7. She was, however, well adjusted to her illness and disability and there was no mood disturbance. There was complete blindness with optic atrophy in both eyes. Eye movements and other cranial nerves were normal. There was mild pyramidal weakness but marked cerebellar ataxia in both upper limbs as well as a spastic paraplegia. Pain, vibration and joint position sense was absent below T2 level and in the fingers. She was doubly incontinent. She appeared to have dry eyes and mouth and Schirmer's test confirmed poor tear secretion.

Investigations at another hospital including a blood count, ESR, VDRL, routine CSF analysis, myelography and CT brain scan revealed no abnormality. Further investigations at Queen Mary Hospital showed a mild normochromic normocytic anaemia and a normal ESR. The antinuclear factor (ANA) was twice positive at a titre of 1:50, but the rheumatoid factor, anti-DNA and anti-ENA antibodies were repeatedly negative with normal C3 and C4 levels and serum immunoglobulins. Serum and CSF viral serology was negative. CSF analysis showed 4 lymphocytes/μl, protein 0.4 g/l, glucose 3.6 mmol/l, IgG elevated at 0.068 g/l (normal <0.055 g/l), IgA normal at 0.007 g/l and undetectable IgM. The IgG/total protein ratio was elevated at 17%, but oligoclonal bands were not present. In the CT brain scan, there was a nonenhancing hypodensity measuring 1 cm in diameter in the corona radiata on the right. VEPs to full-field checkerboard stimulation were absent, BAEPs were within normal limits and SSEPs revealed impairment of posterior column conduction.

The clinical picture strongly favoured clinically definite MS, although the presence of a mild sicca syndrome and a low ANA titre raised the possibility of connective tissue disease. Four months following transfer, she developed haemoptysis. Chest radiographs showed miliary mottling, and a sputum smear was positive for tubercle bacilli. The concomitant presence of miliary tuberculosis thus explained the weakly positive antinuclear factor and anaemia. She received a course of antituberculous therapy. Three months later, she developed septicaemia from urinary tract infection and died despite vigorous antibiotic therapy.

Autopsy limited to the brain and spinal cord was performed 2 days after death. Other organs and the skeletal muscles were not available. The brain weighed 1066 g which was within the lower limit of the normal range for a body height of 140 cm. The basal cerebral arteries showed no significant atherosclerotic changes. The skull, dura and leptomeninges were intact. Both optic nerves and chiasma were atrophic. The nerves and part of the adjoining retinae were also removed. All other cranial nerves were unremarkable. The pituitary gland was essentially normal. The entire length of the spinal cord was dissected. Both the cervical and lumbar enlargements were reduced in size with obvious atrophy of the conus medullaris and its roots. The thoracic segment was not only reduced in size, measuring 4 mm in the largest diameter, but also appeared soft and necrotic.

Coronal sections of the brain were made after adequate fixation. The ventricles were not dilated. There was a small area of greyish discolouration between the angle of the lateral ventricle and the right caudate nucleus. Careful examination of the rest of the cerebral hemispheres, midbrain, pons, medulla and cerebellum did not show classical chronic plaques or other pathological changes. After fixation, the spinal cord was examined by transverse sections at many levels. These revealed conspicuous softenings, more severe on the right in the cervical and lumbar regions, but bilateral at the thoracic cord, affecting both the anterolateral and posterior columns.

Myelin staining of the selected brain sections confirmed a shadow plaque between the angle of the lateral ventricle and the right caudate nucleus, but no additional lesions were identified. The shadow plaque consisted of diffusely distributed, thinly myelinated fibres. Sections of the optic nerves showed extensive areas of demyelination which were not demarcated (fig. 1A, B). The lesions were hypercellular, with abundant hypertrophic astrocytes, and were accompanied by florid perivascular mononuclear cell infiltrates, although plasma cells were not detected either in the lesions or the meninges. A few scattered foamy macrophages could be identified in the background (fig. 2). A Bodian silver stain in this demyelinated lesion still showed some preservation of axons. The spinal cord sections from the cervical and lumbar segments revealed similar changes and in addition marked necrotic changes especially in the thoracic segments (fig. 3). Here the anterior horns were involved with almost complete loss of the large motor

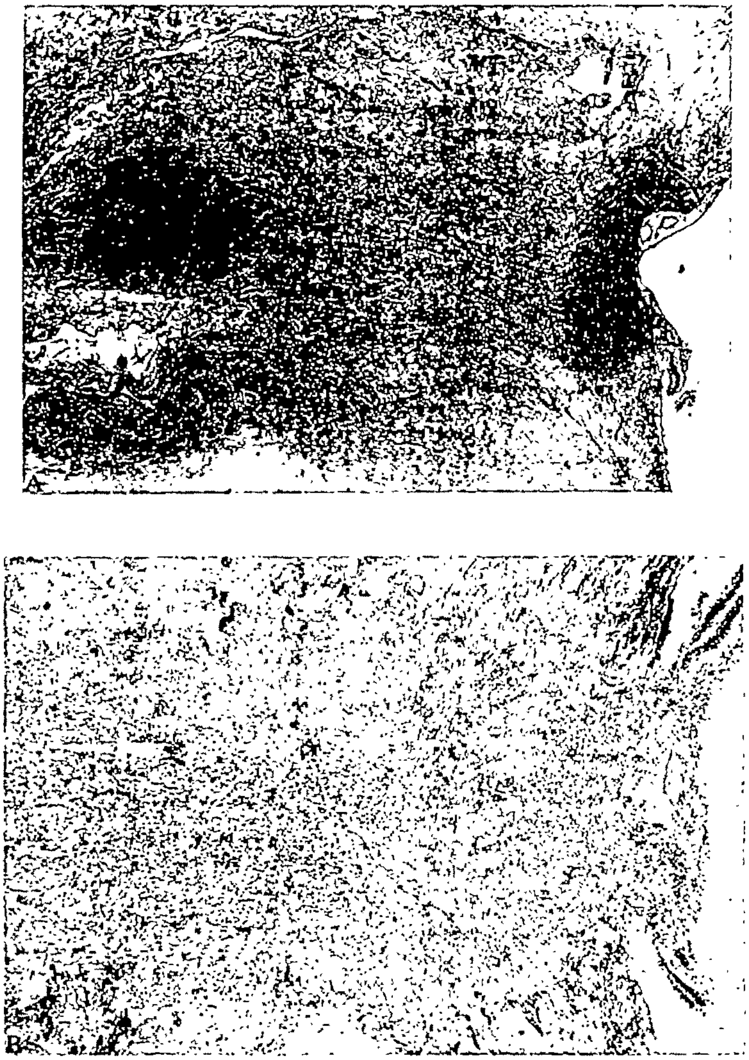

FIG. 1. Optic nerve through the disc, showing a nondemarcated, hypercellular lesion with marked demyelination. A, haematoxylin-eosin, B, cresyl violet/Luxol fast blue, ×5.

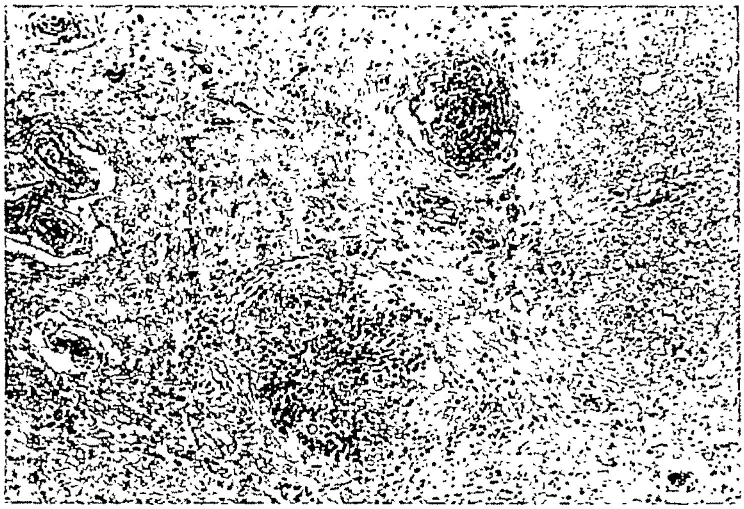

FIG. 2. Optic nerve showing prominent perivascular mononuclear cell infiltration (*below*) with abundant hypertrophic astrocytes (*above*). Haematoxylin-eosin, ×50.

neurons. Elsewhere the posterior and lateral columns were mainly involved but lesions were not sharply defined. Histologically, the perivascular mononuclear cell infiltrates were florid, and foamy macrophages were much greater in number, but plasma cells were absent. On staining with cresyl violet-Luxol fast blue, the lesions were observed to extend for considerable distances into the surrounding white matter, which was often hypercellular with a proliferation of astrocytes. Random sections of the conus medullaris showed uniform myelin loss and similar changes were also seen in the nerve roots. These changes were considered to be secondary to the more rostral lesions. No vasculitic lesions were detected in the neural tissues.

The diagnosis of MS in this patient was therefore confirmed at autopsy, the first documented case in the Hong Kong Chinese. The neuropathological features in this case with prominent necrotic changes are well recognized in some Oriental cases (*see* below), although not typically encountered in Caucasians.

Case 6 (CDMS)

C.L.W., a 35-yr-old housewife, was referred in April 1986 because of an exacerbation of MS. In 1972, at the age of 21 yrs, she developed subacute bilateral visual loss with eye pain, followed by paraesthesiae and severe weakness in all 4 limbs and urinary retention. Devic's disease was diagnosed and she was given a short course of ACTH. She made a gradual but remarkable recovery (from Kurtzke Scale 8 to 2) over a 6 month period and was able to continue her work as an immigration officer. Two years later, she experienced a relapse with cervical cord involvement, presenting as moderate tetraparesis with sensory and sphincter disturbance. She had a similar relapse after another 2 yrs. On each occasion a short course of ACTH was given and she made a good

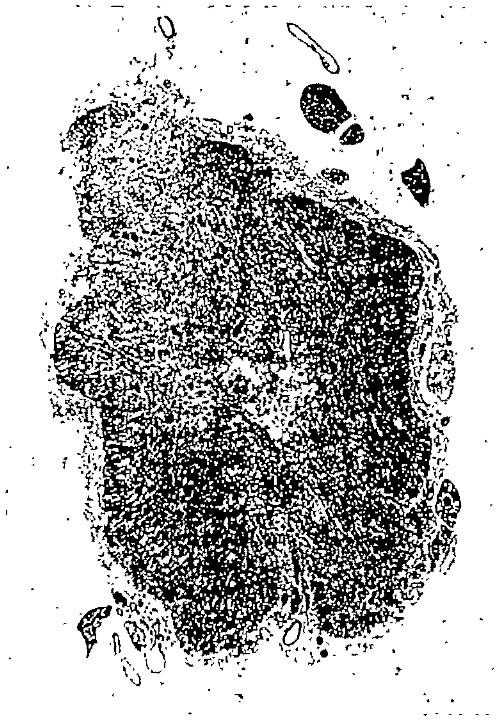

FIG. 3. Thoracic spinal cord (*anterior lowermost*), showing marked atrophy and extensive areas of necrosis, involving both the anterior and posterior columns, more severely on the right (*left of figure*). The anterior horns are totally obscured. Haematoxylin-eosin, ×5.

recovery. However, she decided to leave her job because of easy fatiguability, particularly in summer months.

She remained well until a third relapse in April 1986. Vision in her right eye became blurred over 2 wks, followed by visual impairment in the left eye, and weakness and unsteadiness of the left arm and leg. On examination, she was somewhat euphoric but cognitive functions were normal. VAR was reduced to finger counting and VAL 6/9. There was a central scotoma on the visual field of her left eye and temporal pallor in the right optic disc. Mild pyramidal weakness with moderate ataxia was present in the left upper and lower limbs. Sensation was intact and Lhermitte's sign was negative. The optic nerves and brainstem-cerebellum were therefore affected on this occasion.

Blood counts, biochemistry, VDRL, autoantibody screening, serum immunoglobulins and viral titres were normal. CSF analysis showed 3 lymphocyte/μl, total protein 0.46 g/l, IgG 0.068 g/l, IgG/total protein 14.8%, IgA 0.006 g/l, IgM undetected, and positive oligoclonal bands; viral titres, in particular those of measles and HTLVI, were not elevated. CT revealed low attenuation in periventricular white matter bilaterally which was prominent around the occipital horns of the lateral ventricles.

A 10 day course of dexamethasone was started and recovery was again good (from Kurtzke Scale 6 to 2 over 5 wks), but 5 months later, she had a further attack of bilateral optic neuritis which took 3 wks to resolve. In May 1987, she had to be readmitted because of frequent paroxysmal attacks of severe pain and dysaesthesiae in the left arm. The symptoms were subsequently controlled with carbamazepine.

This case illustrates the characteristic relapses and remissions of MS. The presentation at onset and in the third relapse with bilateral optic nerve and spinal cord involvement within a month would qualify for the label of Devic's disease. Despite the severe symptomatology during exacerbations, the recovery was near complete with only mild residual deficits. Another notable feature was the paroxysmal pain which is believed to occur more commonly in Orientals than in Caucasians (Shibasaki *et al.*, 1981).

DISCUSSION

It was a long-held impression that classical MS was either very rare or nonexistent in the Hong Kong Chinese, and that Devic's disease was the major demyelinating disorder of the CNS. However, with the rapid development of the neurology specialty in recent years, this view has been revised. The number of trained neurologists has now exceeded 20, and all major hospitals have access to a neurological service. Moreover, essential investigative facilities such as CT, evoked potentials, CSF immunoglobulins and HLA typing have become widely available and at only nominal charges at public hospitals. In addition, the referral pattern of general practitioners has changed and neurological disorders are now referred to neurologists rather than to general physicians, orthopaedic surgeons, neurosurgeons or psychiatrists. As a result of increased awareness, more MS cases, mild and severe, have been diagnosed. Since the diagnosis of MS is primarily clinical, there being no confirmatory laboratory tests, case ascertainment is crucial. In this survey, therefore, we assessed every case submitted and took care to enrol only cases fulfilling the criteria of Poser *et al.* (1983). Other conditions, particularly connective tissue disease, were rigorously excluded. Hence, one patient with systemic lupus erythematosus and another with the sicca syndrome, both presenting with separate episodes of spinal cord and optic nerve lesions, were excluded.

The prevalence of MS in Hong Kong is 0.88 per 10^5 population. The earlier Oriental and Caucasian series, using older criteria such as those of Schumacher *et al.* (1965), did not allow for paraclinical evidence of lesions, whereas the present study accepted paraclinical evidence. Thus our prevalence rate is likely to be greater simply because of the difference in diagnostic criteria. On the other hand, it must be emphasized that our estimate is a minimum one, since better case ascertainment will increase the prevalence rate, as illustrated by a recent review of all epidemiological studies in the United Kingdom published since 1931 (Swingler and Compston, 1986). This is certainly true for Hong Kong where awareness of MS and the availability of neurological services still lag behind the developed countries. With these provisos, the MS prevalence in Hong Kong is of the same order as in Taiwan (0.88 per 10^5; Hung *et al.*, 1976); Korea (2 per 10^5; Kurtzke *et al.*, 1968) and Japan (1–4 per 10^5; Okinaka *et al.*, 1960; Okinaka and Kuroiwa, 1966; Kuroiwa *et al.*, 1975, 1983). Such prevalence rates are much lower than in Caucasoid populations, in which the prevalence ranges from 6 in Spain (Oliveras *et al.*, 1968), 7 in Houston, USA (Chipman, 1966), 42 in Northumberland, England (Poskanzer *et al.*, 1963), to as high as 309 in the Shetlands and Orkneys (Poskanzer *et al.*, 1980).

Does the clinical picture of MS in Hong Kong Chinese differ in any way from other Chinese series, or from other Oriental and Caucasoid populations? Comparisons presented in Tables 2–6 reveal no major differences. There is a female preponderance in all series, the female to male ratio of our CDMS patients being somewhat higher (2.9:1) than in the other series (ranging from 1.3 to 2.1:1). The mean age of onset of symptoms is between 29 and 33. The mode of onset is either acute or subacute in the majority, and the proportion of patients with an insidious onset is around 10% in all Chinese series. Familial occurrence is rare in the Chinese, only 1 case having been reported in the Beijing series (Zhao *et al.*, 1979). In the Japanese, familial occurrence is slightly higher at 2% (Kuroiwa *et al.*, 1975), whereas a much higher incidence of 6.5 to 10% is found in Caucasians (McAlpine *et al.*, 1972; Poser *et al.*, 1979; Shibasaki *et al.*, 1981).

The initial symptoms in our patients do not appear to be markedly different from those of other series. Visual loss occurred in 37% of the CDMS patients and in 31% of the Combined patients. These figures are similar to the Beijing and German series, higher than the British series, but lower than the Taiwan and Japanese series. Diplopia and sphincter disturbance appear to be more common in the present series, while motor and sensory disturbance differ little from others. Because of the variation in emphasis, it is difficult to draw firm conclusions. However, the neurological symptoms and signs encountered during the course of disease can be interpreted with more agreement between different investigators since these are time-honoured observations. Thus Table 4 shows that the major clinical features are present in both Caucasian and Oriental patients with a similar frequency. Spinal cord symptomatology was most frequent, followed by the optic nerves, brainstem-cerebellum, and cerebrum. There is, however, a major difference in the Caucasian series in that ataxia was observed in over 80%, in contrast to 24–55% in the Oriental series. The Devic's presentation was encountered in 3 to 8% of Oriental patients but not in Caucasians. Paroxysmal pain with or without spasm was present in 17% of our CDMS patients and probably originated from the spinal cord lesions. Our findings are similar to data of other Oriental series (Shibasaki and Kuroiwa, 1974; Kuroiwa *et al.*, 1975, 1977; Hung *et al.*, 1976; Zhao and Liu, 1979; Zhao *et al.*, 1979; Shibasaki *et al.*, 1981) and confirm the increased frequency of this symptom in comparison with Caucasians. Matthews (1958, 1975) pointed out that such paroxysmal disturbance may arise from the brainstem or spinal cord and suggested the mechanism of lateral ephaptic spread of axonal excitation within the demyelinated plaques.

In line with the minor variations in clinical features, the frequency with which sites of clinical lesions were identified is similar to all Oriental and Caucasian series (Table 5). Thus the optic nerves, spinal cord, brainstem and cerebellum were more often involved, whereas the cerebrum was least affected (18 to 40%).

In conjunction with these observations, the broad similarity in the clinical course and disability between this and other series would challenge previously held impressions about Oriental MS. It was suggested that visual impairment at onset, predominant involvement of the optic nerves and spinal cord, and relatively rapid progression were typical of MS in Orientals (Okinaka *et al.*, 1958; Kurtzke *et al.*, 1968; Mathew *et al.*, 1971; Kuroiwa and Shibasaki, 1973; Kuroiwa *et al.*, 1975, 1977; Singhal and Wadia, 1975; Hung *et al.*, 1976). A likely explanation for this view is underdiagnosis, especially of mild cases. Since MS is an uncommon condition in Orientals, and since the neurological service was relatively undeveloped a decade or so previously, it is not surprising that only the relatively severe and typical cases were diagnosed. The present study made a rigorous attempt to trace all cases. The findings suggest that the previous impressions of major differences in the clinical pictures of Chinese and Caucasian patients are more apparent than real.

The pathological changes in MS are well defined in Caucasians (Allen, 1984). These consist of varying numbers of sharply defined sclerotic plaques, especially in the periventricular region and the lateral white column of the spinal cord. Histologically, these plaques appear as a mass of fibrous astrocytes and processes. In our single autopsy case, the lesions were mainly confined to the optic nerves and spinal cord, there being only one shadow plaque in the cerebrum. Other notable features were hypercellularity and perivascular mononuclear cell infiltration in the optic nerve and spinal cord lesions, and in addition marked necrotic changes in the spinal cord. The intensity of cellular infiltration and the degree of necrosis are unusual autopsy findings in Caucasians with MS, except in more recent, active MS lesions. However, these features have been reported not uncommonly in Japanese patients (Okinaka and Kuroiwa, 1966; Shibasaki and Kuroiwa, 1969, 1973), in Chinese (Hung *et al.*, 1976; Guo, 1979; Zhao and Liu, 1979) and in South East Asian countries (Gwee and Ransome, 1973; Selby, 1973; Vejjajiva, 1973). Because of these features, the diagnosis of Devic's disease was often made in such patients, especially where there were bilateral optic nerve and spinal cord symptoms. With regard to the Chinese patients, Guo (1979) summarized the pathological features in 2 personal cases and 8 in the literature. In most cases the lesions were disseminated and were found in descending order of frequency in the cerebrum, brainstem, spinal cord, cerebellum and optic nerves. Softening, necrosis, astrocytic proliferation and perivascular lymphocytic infiltration were common. The presence of plasma cells in the lesions was not alluded to.

To what extent do the findings in Chinese contribute to an enhanced understanding of MS? Allowing for certain modifications of the clinical and pathological features, the disease is undoubtedly the same in both Chinese and Caucasoid populations. However, the prevalence of the disease in Chinese is lower than in Caucasians, and there is an absence of familial disease. The CSF IgG level and IgG/total protein ratio are elevated in a much smaller proportion of Chinese than in Caucasians (Thompson, 1977; Walsh and Tourtellotte, 1983). The detection rate of CSF oligoclonal IgG bands in Chinese is low: 33% in CDMS patients reported in this paper and 45.8% in Mainland Chinese (Ai and Zhao, 1983). These figures are similar to the figure of 45% reported in Japanese

(Iwashita and Kuroiwa, 1980; Tabira *et al.*, 1982) but are significantly lower than the 90% reported in Caucasians (Walsh and Tourtellotte, 1983). In both Chinese and Japanese, the incidence of positive oligoclonal bands appears to be higher during the active rather than the inactive stages of the disease (Ai and Zhao, 1983; Tabira *et al.*, 1982), whilst in Caucasians there is a remarkable tendency for oligoclonal bands to remain stable irrespective of disease activity and treatment (Olsson and Link, 1973; Olsson and Nilsson, 1979; Baumhefner *et al.*, 1979; Bloom, 1980). Unlike Caucasians, in whom HLA-DR2 is strongly associated with MS (Batchelor *et al.*, 1978; McDonald, 1984, 1986; Tiwari and Terasaki, 1985), such association is not found in Chinese patients (Pei *et al.*, 1986; Hawkins *et al.*, 1988). Could this be an important factor in explaining the complex pathogenesis of MS?

It is now accepted that genetic factors play a role in the pathogenesis of MS, the best documented being those encoded by genes in the HLA region of the sixth chromosome (Compston, 1986; McDonald, 1986). Moreover, the major histocompatibility complex in which these genes are located plays an essential role in modulating the immune response. Oligoclonal IgG in the CSF represents abnormal synthesis of gamma globulin in the CNS and therefore strongly implicates an immune mechanism in the pathogenesis of lesions. We suggest that HLA-associated factors are involved in this mechanism by determining the consequences of the immune response following an environmental assault on a host. In turn, these HLA-associated factors determine the susceptibility of particular hosts to develop the lesions of MS. At least 2 DR2 variants with different DNA structure exist in Caucasians (Nishimura *et al.*, 1984) and Chinese (Kohonen-Corish *et al.*, 1986). We suggest that the association of MS with DR2 and the occurrence of oligoclonal bands in the CSF of patients are related phenomena and that the genes which determine the production of oligoclonal bands may be related to genes which determine one or more variants of HLA-DR2. The absence of a DR2 association with MS in Chinese might then reflect the rarity in this population of such a DR2 variant which occurs in other populations and which is associated with genes determining the production of oligoclonal bands following environmental assault. Before such a hypothesis can be accepted, a prima facie case has to be established that the HLA-DR2 genes in Chinese and Caucasian patients are different at the DNA level. Investigations into this aspect are currently in progress. Should the case be proven, further insight into the origin of MS could be gained.

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LOSS OF MEMORY FOR PEOPLE FOLLOWING TEMPORAL LOBE DAMAGE

by ANDREW W. ELLIS, ANDREW W. YOUNG *and*
EDMUND M. R. CRITCHLEY

(From the Departments of Psychology, Universities of York and Lancaster, and the Department of Neurology, Royal Preston Hospital, Lancashire, UK)

SUMMARY

A 40-yr-old woman, K.S., is reported, who shows a severe loss of memory for people following a history of epilepsy and right anterior temporal lobectomy. Despite this memory problem, K.S. is not clinically amnesic, has a Memory Quotient of 122 on the Wechsler Memory Scale in line with her IQ of 119, and performs well on conventional tests of recognition and recall. She does not have a generalized semantic memory deficit for living things, but her deficit extends beyond people to include famous animals, buildings and product names. Autobiographical memory is good, except where memory for people is concerned. The nature of the memory store that is impaired in K.S. is discussed, as are the implications of her case for theories of the organization of long-term memory.

INTRODUCTION

In recent years an increasing number of reports have appeared of patients suffering from what have been termed semantic memory disorders. These disorders of long-term memory are rather different from traditional amnesia, affecting such aspects as knowledge of the nature and uses of objects and the meanings of words. In many of the reports, semantic memory is not uniformly impaired but is disrupted more for one class of material than another, or for objects encountered in a particular sensory modality. This has led to proposals that semantic memory may be subdivided either by category or by modality of input (for reviews, *see* Shallice, 1987; Warrington and McCarthy, 1987; Riddoch *et al.*, 1988).

As an example, Warrington and Shallice (1984) reported the case of a patient, J.B.R., who showed dramatically better performance on tests involving inanimate objects than on tests involving living things. The tests included object-picture naming, defining named objects, and picture-word matching. Thus J.B.R. could define 'compass' as 'tools for telling direction where you are going', but responded 'don't know' to the word 'parrot'. Sartori and Job (1988) provided a detailed report of a similar case. Patients who show the converse pattern of better performance on living than nonliving things have also been reported (Warrington and McCarthy, 1983, 1987). Warrington and Shallice (1984) noted that living/nonliving may not be the correct characterization of the relevant dimension here, and proposed that a distinction between objects known primarily for

Correspondence to: Professor Andrew Ellis, Department of Psychology, University of York, York Y01 5DD, UK.

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their function and objects known through their sensory properties may be a closer approximation, but these data certainly suggest that the semantic system is organized, and possibly subdivided, along categorical lines.

In this paper we report the case of a patient, K.S., with memory problems following a history of temporal lobe epilepsy and right temporal lobectomy. She is not amnesic in the conventional sense: she has a memory quotient on the Wechsler Memory Scale which matches her IQ, and she remembers such things as digit sequences and complex visual figures at normal levels. Despite that, she has great difficulty remembering people in the absence of a more general semantic memory disorder for living things. We present a detailed case study of K.S., investigating which areas of memory are impaired and which are preserved, and show that although memory for people is what causes her greatest difficulties, her disorder is not entirely specific for people.

CASE HISTORY

K.S., a right-handed woman, was born one month prematurely in 1947. There was a family history of epilepsy: her paternal grandmother and cousin both had major seizures. At the age of 11 yrs she passed the selection examination required for entry to the local Grammar School. She left secondary school with 8 'O' level and 3 'A' level examination passes, entered University in 1965 and graduated in 1968 with an upper second class honours degree in Classics. Since graduating she has worked, and continues to work, as a librarian.

Around 1961, K.S. first began to suffer from epileptic seizures. At the time these consisted of a spot of light in the right visual field which seemed to get bigger, to move across to the left and to give way to a laughing face or some other frightening image. The seizures were initially controlled by anticonvulsants, but they became uncontrolled in 1972. EEGs taken at intervals between 1970 and 1978 showed persistent paroxysmal complexes of polyspike and wave well lateralized to the right and maximal in the temporal area. A right temporal lobectomy was performed in 1973 with removal of the anterior 6.5 cm. The operation extended up to the sylvian fissure, including area T1, and centrally to include the hippocampus and amygdala. Postoperatively her seizures reduced, and were further controlled with antiepileptic drugs, but K.S. experienced bouts of depression and reported a decline in memory.

A CT scan in 1985 showed only the right-sided craniotomy with no intracranial abnormality other than the ablation of the right anterior temporal lobe, but an EEG carried out at the same time showed a right midtemporal delta focus.

The first reports of memory problems came in 1969, 1 yr after leaving University. In 1971, still 2 yrs before her temporal lobectomy, she claimed that her memory was 'ordinary' by comparison with its premorbid excellent level. An account written by her in 1977, 4 yrs after the operation, records feelings of forgetfulness, a reluctance to trust her memory, loss of confidence, and problems sustaining conversational interactions. In 1987–8, when the tests reported below were carried out, K.S. believed that her memory had grown worse in the previous few years. Writing in May 1987 she commented that 'proper names (are) becoming impossible to remember, and this is very embarassing socially. It makes conversation less possible. I can't remember names of people in time and often when given a name it means nothing. This is always happening for some names. . . . Trying to remember causes a complete blockage which is irritating. . . . When reading books or watching serials on television I forget details and characters, and continually need to retrace stories.' More generally, she commented that she had 'no real power of retention of new knowledge' and a 'less efficient power of recall', complaining of 'uncertainty about my memory being right'.

K.S.'s inability to remember people is dramatic and will be analysed further below, but some impression of the severity of the deficit can be gleaned from the fact that although she watches the television news every day, she had no idea when asked in November 1987 who were Sarah Ferguson (The Duchess of

York), Boris Becker or Luciano Pavarotti. This last failure is doubly noteworthy because K.S. has had a keen interest in classical music. She now complains that although she can recognize pieces of music and can place them in a style or period, she can no longer remember the titles of the pieces or who wrote them, an inability which she finds extremely frustrating.

K.S.'s private life has been severely affected by her condition. Though probably always a fairly shy person, she is now very reluctant to engage in interactions for fear that individuals will be mentioned whose names she should recognize but does not. She also finds it embarrassing when people recognize her but she fails to recognize them. This does not happen for people she encounters very regularly but occurs for people she meets rather less often. In her work as a librarian, problems remembering authors and clients have meant that she has had to withdraw to a more clerical position than the one she previously occupied.

At the time of testing, K.S. had suffered from a recurrence of seizures. These included visual hallucinations of scenes such as gardens. These hallucinations were sometimes accompanied by odours, but never sounds. The scenes are described as lasting about 30 s and as often being superimposed on central vision with peripheral vision remaining normal. K.S. remained aware of what was going on around her throughout.

Clinical investigations

Tested in 1987, K.S.'s Performance IQ on the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955) was 113, and her Verbal IQ was 122 (Overall IQ = 119). Her score on the New Adult Reading Test (NART; Nelson, 1982) indicated a premorbid IQ of 120, the same as her present IQ. On the Wechsler Memory Scale (Wechsler and Stone, 1945) she obtained a Memory Quotient of 122, commensurate with her IQ. K.S.'s performance on the various subtests of the WAIS and the Wechsler Memory Scale are shown in Table 1. She performed perfectly normally for a person of her age and IQ on memory tests

TABLE 1. K.S.'s PERFORMANCE ON THE SUBTESTS OF THE WECHSLER ADULT INTELLIGENCE SCALE AND THE WECHSLER MEMORY TEST

Wechsler Adult Intelligence Scale (scaled scores)	
Information	13
Comprehension	14
Arithmetic	14
Similarities	14
Digit span	14
Vocabulary	14
Verbal IQ = 122	
Digit symbol	7
Picture completion	13
Block design	14
Picture arrangement	10
Object assembly	9
Performance IQ = 113	
Full scale IQ = 119	
Wechsler Memory Scale	
Information	5
Orientation	5
Mental control	8
Passages	13
Digits	12
Visual reproduction	14
Associative learning	16
Memory Quotient = 122	

involving the recall of passages of text, reproduction of complex visual figures, paired associate learning for words, and immediate forwards and backwards recall of digit strings. Copying of the complex Rey-Osterreith figure (Rey, 1959) was perfect (score 36/36), and delayed recall after 45 min was within the normal range (score 15/36).

K.S. had a digit span of 8 for immediate recall of digits presented auditorily at a rate of 1/s. In a supraspan learning task, a sequence of 12 digits was similarly presented auditorily at a rate of 1/s, with a request to repeat the string after each presentation. A criterion of 3 successive correct repetitions was achieved after 7 repetitions (not counting the criterial trials). A group of 10 normal female controls matched on age and education level required a mean of 7.1 presentations to achieve criterion (SD = 2.42). Her learning and recall of digit sequences is thus entirely normal.

K.S.'s immediate recall span for spatial positions on the Corsi blocks test was 5. Supraspan learning of a 9-item sequence was assessed with a presentation rate of 1 item/s and immediate recall after each presentation. She required 4 presentations to reach a criterion of 3 successive correct repetitions. The 10 matched controls required a mean of 3.5 trials to reach criterion (SD = 0.97), showing K.S.'s learning and recall of a Corsi block sequence to be entirely normal. Three hours after memorizing the Corsi sequence K.S. recalled it correctly and unassisted at the first attempt.

The Warrington Memory Test (Warrington, 1984) assesses forced-choice recognition memory for words and unfamiliar faces. K.S. obtained a very good score of 48/50 for the words. Her score of 39/50 for unfamiliar faces is less impressive, but is still only 1/SD below the mean for Warrington's normal control subjects. There were other tests involving face processing that K.S. performed competently despite her difficulties with famous faces. In the Benton Test (Benton and Van Allen, 1968) the subject is shown a black-and-white unfamiliar face and is required to indicate which of 6 photographs below the target face is a picture of the same person taken from a different angle and with a different expression. K.S. obtained a normal score of 45 on this test. On a test requiring her to judge whether two different faces have the same or different expression she scored 28/32 (1 SD below the mean of normal controls tested at the Radcliffe Infirmary, Oxford). On an expression labelling test which requires the subject to name the expressions on faces she obtained a score of 20/24, which is again well within the normal range.

Subjective memory assessment

In 1987 K.S. was given two subjective memory questionnaires, the Inventory of Memory Experiences (Herrmann and Neisser, 1978), and the Subjective Memory Questionnaire (Bennett-Levy and Powell, 1980; Bennett-Levy *et al.*, 1980). Subjects' responses to such questionnaires are not always reliable, but we include them here because of the good general agreement between the results of formal tests and K.S.'s own assessment of which aspects of memory cause her the greatest difficulties. In her responses to the questionnaires she did not claim that her memory is poor in all situations. She did, however, rate her memory as poor on anything to do with people (recognizing faces; remembering where she has met people before and what they do; remembering their names; remembering people's voices and what they look like; remembering details of characters in books). Other aspects of memory rated as poor include being unable in conversations to think of things to say, being unable to remember the content of conversations, being unable to remember jokes or stories, forgetting that she has done something and thus starting to do it again, forgetting why she set off to do something, forgetting to return things she has borrowed, forgetting to relay messages, thinking she does not know something when she does, forgetting the names of streets and houses, forgetting the themes of books she has read, and forgetting directions of how to get somewhere. Many of these reported problems involve memory for people in some form or other. For example, it is not surprising that she has difficulty thinking of things to say in conversations if she cannot remember pertinent details about people she is talking to or about people whose names crop up in the conversation.

What appears to be a separate cluster of complaints has to do with being easily distracted and unable to sustain a level of concentration for any length of time. These include being unable to pay attention to what people are saying or to the contents of something that she is reading, daydreaming, and being unable to make up her mind. We have not investigated this aspect of her reported difficulties, nor a tendency to confuse left and right, of which she also complained.

In contrast to these difficulties, K.S. reported no particular problems with memory for the layout of a familiar town, where she has left something, what she went to a shop to buy, telephone numbers (either remembering familiar ones or remembering unfamiliar ones between looking them up in a directory and dialling), the birthdays of members of her immediate family, appointments, tunes or the lyrics of songs, train or bus times, mathematical formulae or conversions, colour codes and the colours of familiar but absent objects such as items of clothing, details of the shoe or clothes sizes of members of her family, and the times of television programmes. In general, this pattern of reported memory problems in some areas but not others agrees with the findings detailed below that she has severe memory problems in cetain domains (most notably people) while retaining a good memory in other domains.

RESULTS

Memory for people

K.S. does not have an anterograde amnesia as assessed by conventional tests involving the learning of verbal or pictoral material. Although she complains of a general loss of confidence in her memory, both the subjective and objective tests indicate that this memory loss is not uniform but is perhaps most severe as it pertains to people. She performs adequately on face processing tasks which do not require her to identify famous faces, but has considerable problems where explicit memory for people is concerned. The tests reported in this section were designed to explore K.S.'s problem with memory for familiar people.

Faces line-up. The faces line-up test contains 20 pictures of very famous (high familiarity) people (e.g., Margaret Thatcher; John Wayne), 20 pictures of somewhat less famous people (e.g., Lucille Ball; Max Bygraves) and 20 pictures of unfamiliar people. The faces are shown singly and the test is untimed. For each face the subject is asked first to rate its familiarity on a scale from 1 (totally unfamiliar) to 7 (highly familiar), then to state the person's occupation and finally to give the name. The series is preceded by 44 practice faces.

The faces line-up test was presented twice, once in May 1987 and again in February 1988. K.S.'s scores on this test are shown in Table 2 together with the scores of 28 normal control subjects tested at the Radcliffe Infirmary, Oxford. K.S. performed better on the high familiarity than the low familiarity faces, but her performance on both is dramatically worse than that of the controls on familiarity, occupation and name aspects of the test. The one respect in which her performance is similar to that of control subjects

TABLE 2. PERFORMANCE OF K.S. AND NORMAL CONTROL SUBJECTS ON THE FACES LINE-UP

		High familiarity faces			*Low familiarity faces*			*Unfamiliar faces*
		Familiarity rating	*Occupation*	*Name*	*Familiarity rating*	*Occupation*	*Name*	*Familiarity rating*
K.S.	May 1987	4.20	10	6	2.20	5	0	1.10
	February 1988	4.30	13	10	1.90	3	1	1.00
Controls	Mean	5.98	18:86	16.25	4.18	13.07	9.39	1.36
	SD	0.51	1.15	2.81	1.63	4.54	4.44	0.45

is that she does not rate the unfamiliar faces as any more familiar than they do, indicating that she does not produce confabulatory responses.

Names line-up. In the names line-up test the subject is presented with the names of the same 20 high familiarity people and the same 20 low familiarity people as are seen in the faces line-up. Twenty unfamiliar names replace the 20 unfamiliar faces of the faces line-up. The subject is asked to rate each name on the same 7-point scale and to provide the occupation for each name.

The results for K.S. and 12 normal subjects are shown in Table 3. The controls for this test are male janitors who work at Newcastle Polytechnic: thus their IQs and educational backgrounds are likely to be lower than K.S.'s. Nevertheless, the pattern which emerges for K.S. is clear. As on the faces line-up test, she performs better on high familiarity than low familiarity names, but is well below the normal subjects on both. She does not, however, rate unfamiliar names as any more familiar than do the normal subjects.

TABLE 3. PERFORMANCE OF K.S. AND NORMAL CONTROL SUBJECTS ON THE NAMES LINE-UP

		High familiarity names		*Low familiarity names*		*Unfamiliar names*
		Familiarity rating	*Occupation*	*Familiarity rating*	*Occupation*	*Familiarity rating*
K.S.		4.70	16	3.15	8	1.10
Controls	Mean	6.27	19.66	5.92	19.16	1.10
	SD	0.63	0.84	0.92	1.14	0.10

Contingencies between line-up tasks. It is of some interest to gauge K.S.'s consistency from one presentation of the line-up test to another. Shallice (1987) has argued that if a patient has suffered a loss of information from a memory store (a 'degraded store' in his terminology), then performance on a set of items should be highly consistent from one occasion to the next because items present in the store should always be available and items lost should never be available. If, on the other hand, the problem is one of the unreliable access to the contents of an intact store, then performance will be less consistent between one occasion and the next.

Consistency can be measured using the contingency coefficient C (Siegel, 1956). For a 2×2 contingency table this statistic varies from 0 (no association) to 0.707 (perfect association). Table 4A shows K.S.'s consistency between two administrations of the faces line-up test in terms of whether or not correct occupations were provided for the faces. The contingency coefficient in this instance is 0.403, which represents a significant ($P < 0.01$) but not particularly high tendency for the same faces to be given correct or incorrect occupations on two occasions separated by about 9 months. Table 4B shows K.S.'s consistency over a 1-month interval between the second administration of the faces line-up and the names line-up tests. Once again this is in terms of her ability to provide occupational information about the celebrities whose faces or names were

TABLE 4. ASSOCIATION BETWEEN TWO ADMINISTRATIONS OF THE FACES LINE-UP TEST (A) AND BETWEEN ONE ADMINISTRATION OF THE FACES LINE-UP AND THE NAMES LINE-UP TESTS (B) IN TERMS OF FAMOUS PEOPLE FOR WHOM OCCUPATIONS COULD OR COULD NOT BE SUPPLIED

		Faces: May 1987	
A		*Correct*	*Incorrect*
Faces: February 1988	Correct	11	5
	Incorrect	4	20

		Faces: May 1987	
B		*Correct*	*Incorrect*
Names: June 1987	Correct	13	11
	Incorrect	2	14

presented. Note that K.S. rarely gave incorrect occupational information, so that 'incorrect' here nearly always means that she was unable to provide any occupation information at all. The contingency coefficient between the second line-up test and the names line-up test is 0.346. Once again this is significant ($P < 0.05$) but not particularly high.

Famous Voices Test (Meudell *et al.*, 1980). This test requires the subject to recognize the voices of 79 famous people from every decade from the 1930s to the 1970s. K.S. found this test very difficult, recognizing only 6/79 voices. For comparison, the normal subjects in the study of Meudell *et al.* recognized an average of 37.60 voices (SD = 13.72) and the amnesic patients in their study recognized an average of 12.40 voices (SD = 9.20). K.S. thus falls in the amnesic range where famous voice recognition is concerned.

The Famous Personalities Test (Stevens, 1979). This and the following test are of interest because they allow comparison between K.S. and the only other patient we have been able to discover in the literature who resembles her at all closely, namely patient E.D. of Kapur *et al.* (1986), although we should note that E.D. is over 70 yrs old whereas K.S. is only 40.

In the Famous Personalities Test, the subject is presented with 160 names, 100 of which are personalities who were famous at some time during the last 50 yrs. These can be divided into 20 names which are familiar to virtually everyone, plus 20 which are typically only recognized by subjects over 50 (the oldest personalities in the list), 20 which only over 40s usually recognize, 20 recognized only by over 30s, and 20 which, while not being very famous, are capable of being recognized by over 20s. There are an additional 60 unfamiliar names on the list. The subject's task is simply to state whether or not he or she recognizes each name. As such it resembles the familiarity decision part of the line-up tasks.

K.S.'s results on this test are shown in Table 5 together with the results from 5 normal subjects and E.D. (data from Kapur *et al.*, 1986). We will compare K.S. with E.D. in the Discussion. For now we note that K.S. recognized all the very famous names and made relatively few false positive errors to unfamiliar names, but made many more

TABLE 5. NO. OF NAMES RECOGNIZED BY K.S., E.D. AND NORMAL CONTROL SUBJECTS IN THE FAMOUS PERSONALITIES TEST (STEVENS, 1979)*

	K.S.	*E.D.*	*Controls*
Very famous names (n = 20)	20	20	19.5
Names usually recognized by over 20s (n = 20)	15	13	19.4
Names usually recognized by over 30s (n = 20)	9	13	17.8
Names usually recognized by over 40s (n = 20)	3	17	16.6
Names usually recognized by over 50s (n = 20)	1	11	15.2
Fictitious names (false positive errors) (n = 60)	2	0	0.5

* Data on E.D. and controls from Kapur *et al.* (1986).

errors than the normal subjects on the less famous names. This is true of names which could be recognized by the over 20s and over 30s as well as the names of personalities from the more remote past whom K.S., who is 40 yrs old, could be forgiven for not recognizing.

Dead-or-Alive Test. This test, kindly lent to us by Dr N. Kapur, asks the subject to say whether famous people whose names are given are dead or alive, whether they were killed or died of natural causes, and when they died. We used the test to compare K.S. with E.D. K.S. obtained a score of 42 while E.D. scored 54 (out of a maximum possible score of 140). K.S.'s impairment is at least as serious as that experienced by E.D. where memory for people is concerned.

Memory for specific things other than people

We have seen that K.S.'s memory for famous people is very poor, whether memory is tested for faces, names or voices. The tests reported in this section are designed to explore the extent to which K.S.'s memory problem is *specific* to people. We first investigated her knowledge of living and nonliving objects in order to discover whether or not she has a more generalized semantic memory disorder. We then investigated her memory for things which are not people but which are nevertheless singular things with individual names (proper nouns).

Object naming. K.S. was shown drawings of 20 living and 20 nonliving things and was asked to name them. She named correctly 19/20 living things and 20/20 nonliving things matched on familiarity, complexity, and name frequency (Young and Ellis, 1989). K.S.'s sole error was to misname a picture of an ant as a 'beetle'.

Category membership decisions for living and nonliving things. In the Introduction we mentioned cases of semantic memory deficits that are more pronounced for living than nonliving things. It is important to know if K.S.'s memory problems extend beyond people to other living things such as birds or flowers. This experiment investigated the intactness or otherwise of K.S.'s semantic knowledge of living and nonliving things.

On each trial of the experiment she was presented with a category label in capital letters (e.g. BIRD or FURNITURE) underneath which was a noun which she was either to accept or reject as a member of the category (e.g., swan or cravat). The nouns were taken from the British category structure norms published by Hampton and Gardiner (1983). Five categories of living things were used (birds, fish, flowers, fruit and insects) and 5 categories of nonliving things (clothing, furniture, sports, vehicles and weapons). Ten high typicality and 10 low typicality exemplars of each category were chosen, with the high and low typicality members of the various categories being matched on familiarity.

The 20 positive trials of a particular category (10 high typicality, 10 low typicality) were randomly interspersed with 20 negative trials in a block of 40 trials in which performance on a particular category was assessed. In the negative trials a category label was accompanied by a member of one of the other categories (e.g., BIRD – salmon or FLOWER – sleigh). Each noun was used once as a 'Yes' response (category member) and once as a 'No' response (noncategory member) during the course of the experiment. Stimuli were presented as back-projected slides. Exposure time was 2.5 s per trial, during which K.S. was to make her decision by pressing 1 of 2 horizontally separated buttons. Reaction times were recorded from stimulus onset, and errors were noted.

In terms of the category norms we used, K.S. made 2 errors in the experiment (an error rate of 0.5%), but the 'errors' involved failing to classify a worm as an insect and a coconut as a fruit. In the former case she is absolutely correct, and in the latter case might be given the benefit of the doubt.

K.S.'s mean reaction times are shown in Table 6. This table also shows the results from a patient M.S. with a genuine semantic memory problem that was most pronounced for living things (especially low typicality exemplars), plus data from 4 normal control

TABLE 6. MEAN REACTION TIMES IN ms FOR K.S. IN THE CATEGORY MEMBERSHIP TASK, WITH DATA FROM PATIENT M.S. AND NORMAL SUBJECTS

	High typicality members			*Low typicality members*			*Nonmembers*		
	K.S.	*M.S.*	*Normals*	*K.S.*	*M.S.*	*Normals*	*K.S.*	*M.S.*	*Normals*
Living things									
Birds	673	1412	579 (90)*	679	2026	644 (107)*	801	2070	695 (88)*
Fish	719	1443	625 (107)	990	1990	678 (109)	907	1866	680 (55)
Flowers	706	1832	652 (120)	750	2674	741 (143)	765	2019	704 (111)
Fruit	808	1205	588 (122)	940	2063	675 (108)	914	1663	702 (138)
Insects	755	1552	611 (79)	949	2263	710 (147)	899	2153	669 (97)
Mean	732	1489	614 (98)	862	2203	690 (115)	857	1951	690 (88)
Nonliving things									
Clothing	800	1148	646 (120)	854	1286	644 (116)	1092	1622	686 (116)
Furniture	712	1289	608 (73)	1038	1716	712 (67)	831	1799	677 (103)
Sports	749	1417	589 (87)	776	1430	629 (91)	791	2033	680 (155)
Vehicles	689	1090	584 (69)	753	1214	596 (59)	817	1430	640 (92)
Weapons	719	1158	664 (72)	954	1565	748 (149)	769	1571	689 (73)
Mean	734	1220	618 (71)	875	1442	676 (80)	860	1691	674 (89)

* Values in brackets are SD.

subjects (undergraduate students aged 20–30 yrs; Young *et al.*, 1989). An analysis of variance carried out on K.S.'s results showed no effect of living versus nonliving ($F < 1$) but a significant effect of typicality ($F(2,16) = 8.34$, $P < 0.01$). Post hoc Newman-Keuls tests showed that Yes responses to High typicality items were faster than Yes responses to Low typicality items which did not differ from No responses to noncategory members.

K.S.'s reaction times were always within 2 SDs of the normal control subjects, her pattern is exactly the same as theirs, and very different from patient M.S. Importantly, she responded as rapidly to living as to nonliving things and shows comparable typicality effects for both. Thus K.S. does not have the generalized semantic memory impairment for living things. This finding is in line with the report of Wilkins and Moscovitch (1978) that patients who have undergone right temporal lobectomy perform well on semantic classification tasks.

Famous animals. K.S. was given the names of 22 real or fictitious animals with individual names (e.g., Lassie; Moby Dick). For each name she was asked to state what type of animal it was. K.S. identified only 9/22 animals. Her errors included Trigger, Dumbo and Red Rum (a very famous English racehorse). In contrast, 10 matched female controls identified an average of 20.7 animals (SD = 1.42). It is clear, then, that K.S.'s memory problems extend to famous individual animals.

Famous buildings, monuments, etc. K.S. was given the names of 20 famous buildings, monuments, etc., and was asked to state in which country each was to be found. Examples are the Kremlin (Russia), The Louvre (France) and the White House (America). K.S. scored 12/20 correct. Ten matched female controls scored a mean of 19.1 (SD = 1.85). K.S. claims always to have been weak on geography, but these results suggest that her memory for singular buildings, monuments, etc., is well outside the normal range.

Old product names. K.S. was given the names of 34 products which were common in her childhood, some of which are still around. Examples are Typhoo (tea), Swan Vestas (matches), Woodbine (cigarettes) and Raleigh (bicycles). For each product name she was asked to state what sort of product it was. K.S. identified 21/34 products. Ten matched female controls identified an average of 33.3 (SD = 1.06), showing that K.S.'s problems extend to products with individual names.

Autobiographical memory

Autobiographical memory is a notoriously difficult thing to study scientifically. We will restrict ourselves here to a few observations on K.S.'s autobiographical memory which seem to be compatible with her being characterized as having a poor memory for people in the context of otherwise good recall.

K.S. was able to give a detailed account of her childhood days. She remembered the house where she lived as a girl, recalling its location, address, and the fact that the family had to move out in order that a motorway might be built across the site. She also described her school life in fair detail, remembering such things as the names of her schools, their uniforms and the routes she travelled to get to them. K.S. appeared to have a quite good memory for people she knew as a girl, describing neighbours, teachers and school friends much better than she now describes colleagues at work. There may thus by some sparing of memories for people encountered in her early life, though the evidence here is only suggestive.

In November 1987, K.S. gave an account of a trip to London taken a few months previously in order to visit a specialist. Once again, the account was detailed except where memory for the people she had met was concerned. Thus she remembered the journey down and the rush to get lunch at the hospital, but could recall none of the people she had met on the way. She also remembered the layout and details of the specialist's room and the things they had talked about, but she had no recollection of what the specialist was like.

Also in November 1987, she described a holiday she had taken with her parents in the summer. She gave a detailed description of the hotel in which they had stayed (including its name, hill-top location and the street it was on), what the weather was like, the journey to the resort (including the town where they had stopped for lunch and the fact that all the shops were closed because it was Sunday), and some of the trips on which they went. She was quite unable, however, to recall anything about any of the other people who were on the 8-day package holiday with them.

K.S.'s autobiographical memory is thus compatible with the evidence from the objective tests which show good memory performance except in certain, fairly well circumscribed areas, most notably memory for people.

DISCUSSION

K.S.'s general intelligence remains high. A comparison of her NART score with her present performance on the WAIS indicates that her IQ has not declined postoperatively. Her verbal and nonverbal short-term memory remain normal, as do many aspects of her long-term memory. Her Wechsler Memory Quotient is 122, and she learns and recalls digit sequences, Corsi block sequences, words, unfamiliar faces, and the Rey-Osterreith figure at normal levels. Semantic memory for living and nonliving things is preserved. Except for people and famous animals with singular names, K.S.'s knowledge of living things is good. She could provide good definitions of names of living things, defining an onion as 'a vegetable; a root like a bulb; orangey-brown' and a daffodil as 'a spring flower grown from a bulb; yellow'. She also named drawings of living things well and showed no evidence of a selective semantic memory problem for living things in the category membership decision task.

Despite her generally good memory, K.S. has severe memory problems in certain areas, especially memory for familiar people. Not all tasks involving people as stimuli are performed badly: judgements of emotional expressions are within normal limits, as is performance on the Benton test of unfamiliar face matching and on the Warrington test of recognition memory for unfamiliar faces. She is severely impaired, however, at recognizing famous faces, names or voices, retrieving knowledge about well-known people, and naming them, though her problems extend beyond faces to famous animals, product names and buildings or monuments.

The deficit is not modality-specific as it would be in, for example, prosopagnosia, but appears to be of a more central nature. We will discuss the possible nature of the deficit in more detail below. For now we would wish to emphasize the general points to emerge clearly from K.S., namely that impaired knowledge of people and certain other singular objects can occur in a patient whose memory for such things as words, word associations, digit strings, spatial positions, unfamiliar faces and complex visual figures is intact. These observations strengthen the case for the existence of multiple long-term memory systems serving different purposes. Long-term memory, like short-term memory and perceptual recognition, is not mediated by a single undifferentiated memory system (see Parkin, 1987; Squire, 1987).

Problems of the sort experienced by K.S. have not previously been commented upon as sequelae of damage to the right temporal lobe. However, because of her longstanding history of epilepsy, the possibility of additional damage involving her left temporal lobe obviously exists. Bennett-Levy *et al.* (1980) and Bennett-Levy and Powell (1980) found significantly lowered subjective memory assessments in temporal lobectomy patients for memory concerning the names of people, the numbers of people's houses, people's voices, the themes of books, and the details of characters in them, although only on memory for faces were reported difficulties worse in right than left temporal lobectomy patients. It is possible that among the patients contributing to group studies of the type carried out by Bennett-Levy *et al.* were individual patients very much like K.S., but this cannot be deduced with any confidence from the group data. We have only been able to identify one patient in the single case study literature who resembles her.

Kapur *et al.* (1986) reported the case of a patient E.D. who had experienced multiple episodes of transient amnesia over a 6-yr period and who has since developed temporal lobe epilepsy (bilateral temporal abnormalities on EEG, with spike and wave discharges more prominent in the left temporal region; N. Kapur, personal communication). E.D. had a full-scale IQ of 103, though the NART suggested a premorbid IQ of around 114. Kapur *et al.* pointed out that this difference might reflect a minor degree of generalized cognitive dysfunction, although more recent testing (N. Kapur, personal communication) has indicated an IQ of 111. He obtained a memory quotient on the Wechsler Memory Scale of 120, with excellent performance on the paired associate learning subtest. Like K.S., E.D. was very poor on memory for people. His performance on the Famous Personalities Test (Stevens, 1979) is shown alongside that of K.S. in Table 5. E.D. was poor on memory for famous voices and for public events (which, of course, characteristically involve people).

Kapur *et al.* interpreted this poor memory for events and people in the context of good performance on the Wechsler Memory Test as evidence that E.D. suffered from a retrograde amnesia without an anterograde amnesia. This may be correct, but we would suggest an alternative possible interpretation of this case. Retrograde memory tests depend heavily on memory for famous people, even when ostensibly testing memory for events. Anterograde memory tests, in contrast, do not involve memory for famous people, involving instead memory for such things as words, digits, or spatial positions. From our perspective, conventional retrograde and anterograde memory tests draw on very different types of memory. Using standard clinical tests it would be hard to distinguish a patient with poor memory for people (and events involving people) from a case of more generalized retrograde amnesia.

K.S.'s loss of memory for people appears to be central in nature. She does not simply have a modality-specific prosopagnosia, but instead shows impaired knowledge about people, however that knowledge is assessed. This suggests that her central store of semantic information about people is impaired (or access to it). She recognizes very famous celebrities better than less famous ones, and in her private life it appears that she recognizes people she meets very regularly better than people with whom she comes into contact rather less often. That said, her memory for famous people whose general occupation and whose name she can supply may not be completely intact. For example, although K.S. could reliably name Mrs Thatcher and give her occupation, when probed a little further she was unable to identify Mrs Thatcher's constituency from a choice of three, and could not recognize the occupation of Mrs Thatcher's father, although the fact that the Prime Minister is a grocer's daughter is well known. The present data do not allow us to arbitrate between an impairment to the semantic store itself versus impaired access to the contents of that store, but we think it at least possible that semantic information about people is registered and stored in her memory but becomes inaccessible unless it is frequently rehearsed (as it would be for very famous celebrities or people she meets regularly in everyday life). Unfortunately, work with K.S. had to be suspended due to a recurrence of generalized grand mal seizures. Because of this, we were unable to tackle the important question as to whether she would have shown 'implicit' knowledge of people that she did not recognize consciously (*see* Young and De Haan, 1988; Hanley *et al.*, 1989).

We have shown that K.S.'s problems extend beyond familiar people to famous animals, buildings and products. We propose that she has suffered damage to a semantic memory system that is critically involved in storing information about familiar people, but which also extends to information about familiar animals, buildings and products. Such a system could be characterized as one specialized for the *storage of information about singular objects*.

Objects can usually be understood and acted upon perfectly well at what has been called the 'basic level' (Rosch, 1978); that is, as *a* building, *a* cat, or *a* packet of tea. As far as we have been able to discern, K.S. has no problems operating with objects at that level. Similarly she has no problem when people can be interacted with in a manner that does not require her to recognize and have knowledge of the person as an individual: she has no problem behaving appropriately towards people when they can be dealt with as *a* nurse or *a* shopkeeper. Where problems arise is when she must recall information about singular objects or people in order to respond appropriately, recalling the country in which a famous building can be found or the occupation of a famous person. Product names are not quite singular but certainly require objects to be differentiated beyond the basic level.

Finally, we have been referring to the memory system that is impaired in K.S. as a semantic system, but it is also clear from her case that it is involved in episodic or autobiographical memories where people are concerned. K.S. remembers events and episodes from day to day and can recall them at length except for details about people she has met, when her memory is very hazy. This would accord with the view that the successful storage and recall of autobiographical memories requires a complex synthesis of memory for particular episodes and more general factual or semantic memory.

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VISUOSPATIAL PROCESSES OF LINE BISECTION AND THE MECHANISMS UNDERLYING UNILATERAL SPATIAL NEGLECT

by SUMIO ISHIAI, TETSUO FURUKAWA *and* HIROSHI TSUKAGOSHI

(From the Department of Neurology, Faculty of Medicine, Tokyo Medical and Dental University, Tokyo, Japan)

SUMMARY

Patients with unilateral spatial neglect fail to report or respond to stimuli contralateral to the lesion which usually involves the right parietal lobe. When asked to mark the centre of a horizontal line, these patients place the mark to the right of the true midpoint. It has been considered that they neglect the left part of the line and bisect the perceived line segment. We investigated the eye-fixation patterns of hemianopic patients with or without unilateral spatial neglect during the bisection of lines, using an eye camera.

Hemianopic patients without unilateral spatial neglect saw the whole line, searching to the endpoint on the hemianopic side, and bisected it correctly. In contrast, left hemianopics with unilateral spatial neglect never searched to the left hemianopic side. Once they fixated a certain point on the right part of the line, they persisted with this point and marked the subjective midpoint there. Taking left homonymous hemianopia into account, the subjective midpoint appeared to be marked, not at the centre of the line segment perceived in the seeing right visual field, but at the leftmost point of it. However, they could appreciate the deviation of the subjective midpoint in the right visual field when forced to fixate the left endpoint of the line. These findings suggest that the left hemisphere has the ability to estimate the midpoint of the line through the right visual field and that visuospatial disorder in the line bisection test is attributable to the pathological change in the right hemisphere.

The results are interpreted to mean that left hemianopic patients with unilateral spatial neglect see a totalized image of a line extending equally to either side of the point where they are going to mark the subjective midpoint. We considered that the right hemisphere completes the line, using the visual input relating to the right part of the line perceived by the left hemisphere.

INTRODUCTION

Unilateral spatial neglect is the failure of brain-damaged patients to report, respond or orientate to novel or meaningful stimuli presented in the side of space contralateral to the lesion, which usually involves the right parietal lobe (Critchley, 1953; De Renzi, 1982; Heilman *et al.*, 1983*b*; Vallar and Perani, 1987). These patients may draw only the right half of a daisy, pick up food from the right half of the plate or cross out lines distributed over a page leaving the lines on the left side.

The line bisection test has long been used for a sensitive measure of unilateral spatial neglect (Schenkenberg *et al.*, 1980; De Renzi, 1982). When asked to bisect a line, the patients place the subjective midpoint to the right of the true centre. Some modifications

Correspondence to: Dr Sumio Ishiai, Department of Rehabilitation, Tokyo Metropolitan Institute for Neurosciences, 2–6 Musashidai, Fuchu City, Tokyo 183, Japan.

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of the task have been made to study the underlying mechanism. Heilman and Valenstein (1979) found it of no benefit to compel the patients with neglect to see the full extent of the line before bisecting it. Performance was significantly better when the line was placed to the right side of the body than to the left. Contrary to this report, Riddoch and Humphreys (1983) showed a marked decrease in neglect when subjects were cued and forced to report stimuli in their neglected field, irrespective of hemispace position. The existence of a cuing effect in the neglected side was supported by observation with the reaction time task used by Posner *et al.* (1982).

In the screening tests for neglect, however, free visual exploration is permitted and the visuospatial processes involved in their execution have not been clarified. We have reported the eye-fixation patterns of hemianopic patients while viewing simple patterns (Ishiai *et al.*, 1987). Hemianopic patients without unilateral spatial neglect showed a compensatory eye-fixation pattern which consisted of repeated searches to the hemianopic side, but those with neglect showed no compensation. Such eye-fixation differences between hemianopic patients with and without unilateral spatial neglect were also considered to occur in the course of line bisection.

For the original version of the line bisection test without cuing, it was expected that patients with unilateral spatial neglect would incorrectly estimate the centre of the line to the right of the true centre, neglecting the left part of the line. However, we do not know whether they bisect the line segment perceived in the seeing right visual field or if they neglect the left side even in this segment. In order to make this point clear, we investigated the relationship between the subjective midpoint and the actually perceived extent, observing the eye-fixation pattern and marking procedure. With a left homonymous hemianopia or 'visual extinction' in the left visual field (Friedland and Weinstein, 1977), a visual stimulus is projected centrally by way of the right visual field. We also examined the patients' right visual field in relation to the ability to appreciate the rightward deviation of the mark on the line.

METHODS

Subjects

The subjects were 21 right-handed hemianopic patients with unilateral hemisphere lesions due to cerebrovascular events. Each subject's visual field was measured by means of a Goldmann perimeter, except for 2 left hemianopic patients with unilateral spatial neglect (indicated by asterisks in Table 1). Although these 2 patients could not be tested by the perimeter because of their unsteady fixation, confrontation testing revealed the presence of a left homonymous hemianopia. All subjects were examined by a cancellation test similar to that of Albert (1973), the line bisection test (Axenfeld, 1915; Schenkenberg *et al.*, 1980) and a figure-copying task. In the cancellation test and the line bisection test, the degree of left unilateral spatial neglect was rated severe, moderate, mild or none according to the scale by Levine *et al.* (1986). In the cancellation test, crossing out the rightmost one-third or less was termed 'severe', crossing out more than one-third but less than the rightmost two-thirds was termed 'moderate', and crossing out more than the rightmost two-thirds, but not the whole, was termed 'mild'. In the line bisection test, neglect was classified as 'severe' if one-fifth or less of the line was to the right of the patient's mark, as 'moderate' if more than one-fifth but less than one-third of the line was to the right, and as 'mild' if more than one-third but less than a half was to the right. For figure copying, we used a drawing of a daisy with blades of grass 6 cm away from it on either side. If the right half of the daisy with the grass on the right or less was drawn, neglect was rated 'severe'; if the number of petals was fewer on the left than the right and the grass on the left was omitted, neglect was rated 'moderate'; if the number of petals was fewer on the left or the grass on the left was omitted, neglect was rated 'mild'. Those who showed mild, moderate or severe neglect in one or more of these three tests were considered to exhibit unilateral spatial neglect. Eight of the 21 patients had both a dense left homonymous hemianopia and unilateral spatial neglect (LVFD N(+)), while the others had only hemianopia; 5 had a left homonymous hemianopia (LVFD N(−)) and 8 right homonymous hemianopia (RVFD N(−)). The scores of neglect ratings are presented in Table 1.

TABLE 1. SUMMARY OF CLINICAL DATA FOR THE HEMIANOPIC PATIENTS

	Age (yrs)	*Sex*	*Hand* used*	*Visual field*	*USN on*			*Hemiparesis*	*Sensory loss*	*Lesion*
					CA	*LB*	*CO*			
RVFD N(−)										
1	52	M	B	RH	−	−	−	−	−	TO
2	76	M	B	RH	−	−	−	−	−	O
3	72	M	B	RH	−	−	−	−	−	O
4	49	M	L	RH	−	−	−	+	+	DTPO
5	53	M	L	RH	−	−	−	+	+	PO
6	54	M	L	RH	−	−	−	+	+	DTPO
7	65	M	L	RH	−	−	−	+	+	DTPO
8	59	F	L	RH	−	−	−	+	+	TO
LVFD N(−)										
1	69	M	B	LH	−	−	−	−	−	O
2	56	F	B	LH	−	−	−	−	−	O
3	60	M	B	LH	−	−	−	−	−	O
4	58	M	B	LH	−	−	−	−	−	O
5	51	F	R	LH	−	−	−	+	+	DTP
LVFD N(+)										
1	80	M	B	LH**	+++	++	+++	−	−	TPO
2	68	F	R	LH	++	+++	+++	+	+	FTPO
3	60	M	R	LH	+	++	+	+	+	TPO
4	52	F	R	LH**	++	+	+++	+	+	FTPO
5	66	M	R	LH	+++	++	+++	+	+	TPO
6	43	M	R	LH	++	+	+	+	+	TPO
7	69	M	R	LH	−	+	++	+	+	TPO
8	43	M	R	LH	++	+	++	+	+	TPO

B = both hands; R = right hand; L = left hand; RH = right homonymous hemianopia; LH = left homonymous hemianopia; USN = unilateral spatial neglect; + mild, ++ moderate, +++ severe; CA = cancellation; LB = line bisection; CO = figure copying; F = frontal; T = temporal; P = parietal; O = occipital; D = deep lesion. *Preferred hand was the right in all subjects. **Visual field was assessed only by confrontation testing.

The LVFD N(+) group of subjects showed moderate or severe neglect at least in one of the three rating scales.

Of the RVFD N(−) group 38%, and of the LVFD N(−) group, 80% were capable of using both hands, whereas only 13% (1:8) of the LVFD N(+) group could use both hands in testing. CT scans were obtained for all hemianopic patients. All the LVFD N(+) group subjects had lesions which involved the right parietal lobe. The extent of brain damage in this group was larger than that in the other groups, as suggested by Hier *et al.* (1983) and Levine *et al.* (1986). Voluntary eye movements to verbal command and manual tracking were not restricted in any subject. They could fixate a point indicated by the examiner. Ten right-handed subjects without neurological deficit served as normal controls (NC). The average age of the subjects in each group was as follows: NC, 61.0 ± 9.7 yrs; RVFD N(−), 60.0 ± 10.0 yrs; LVFD N(−), 58.8 ± 6.6 yrs; and LVFD N(+), 60.1 ± 13.2 yrs. None of these groups differed significantly in age (df = 3,27, F = 0.05). Table 1 presents the clinical data for 21 hemianopic patients.

Recording of the fixation point

We used an eye camera (Eye Mark Recorder type V; NAC Inc.) for recording the fixation point. The technique used with this apparatus is in principle almost the same as the television technique for recording eye movements (Mackworth and Mackworth, 1958). However, for this apparatus, both the scene camera and the eye camera with an infrared light source are set in a head unit of only 830 g weight. This unit is connected to the control unit by three flexible cables. Thus head movements are possible during the recording of the fixation point. The subject can perform the tasks for routine clinical evaluation under nearly natural conditions.

The corneal reflection detected by the eye camera is transduced electronically into the eye mark and then superimposed on the picture from the scene camera. The movements of the eye mark are adjusted so that when the subject looks at known points in the visual scene, the mark lies over these points in the combined eye-scene picture. The visual angle of the scene camera is 60° horizontally. In this field of vision, movements of the fixation point can be recorded linearly with an accuracy of up to 0.4°. The eye-scene picture was recorded with a video tape recorder at a speed of 30 frames/s.

Line bisection test

Each subject was examined with the line bisection test under ordinary conditions except that the eye camera was mounted on the head. A line 20 cm or 15 cm long was drawn horizontally across the centre of plain B5 paper. Three hemispace conditions were examined. For the centre condition, the paper with a line was placed so that the middle of the paper was in line with the middle of the subject's body. For the right hemispace condition, the left edge of the paper was in line with the middle of the subject's body. For the left hemispace condition, the right edge was in line with the middle of the body. Practice trials were performed before the actual recording of the eye-fixation pattern to ensure that the line was not covered by the hand holding the pencil.

After setting the eye camera on the subject's head and calibrating the eye mark, recording of the eye-fixation pattern was started. Each subject bisected 20 cm lines under the centre, right hemispace and left hemispace conditions with the hand ipsilateral to the lesion. The order in which the three hemispace conditions were used was counterbalanced across subjects in each group. The subjects who could use both hands were asked to complete the alternate form of the test with the other hand. The hands used are listed in Table 1. For the normal controls, the right hand was used first. Only hemianopic subjects with unilateral spatial neglect bisected 15 cm lines in the same way. Because these patients occasionally bisect shorter lines more correctly than longer ones (Bisiach *et al.*, 1983; Riddoch and Humphreys, 1983), we considered it necessary to observe the change in the eye-fixation pattern between lines of at least two different lengths. When the subjects bisected the line as required, one trial for each condition was performed so that they would not develop a response set to one condition.

The visual angle of a 20 cm line varied from about 30° to 50°, according to the distance between the subject's eyes and the line on the paper. The combined eye-scene picture was recorded throughout all the trials.

After the line bisection test, the LVFD N(+) group subjects were tested as to the ability to recognize the rightward deviation of their subjective midpoint in the seeing right half of the visual field. They were instructed to fixate the left endpoint of the line, the fixation point being monitored with the eye camera. If the patient could not find the left endpoint, we guided fixation with a finger. They were forced to keep fixating the left endpoint of the line and were then asked about the adequacy of the subjective midpoint.

RESULTS

Eye-fixation pattern

The fixation point always moved on the line during line bisection. Therefore, lateral movement of the fixation point on the line was analysed, reproducing the VTR recording frame-by-frame. Fig. 1 shows a typical eye-fixation pattern for each group under the centre condition with a 20 cm line. Movements of the fixation point were analysed from the time of initial fixation on the line to the time of fixation when the subject began to mark the subjective midpoint.

Rightward or leftward searches by the NC group of subjects rarely reached the right or left endpoints of the line (fig. 1A). Although the fixation point oscillated considerably on the middle part of the line, they could bisect the line correctly. Hemianopic patients without unilateral spatial neglect made several searches to the endpoint of the line on the hemianopic side, that is, the RVFD N(−) patients made rightward searches to the right endpoint of the line and the LVFD N(−) patients vice versa (fig. 1B, C). In this way, they saw the whole line in their seeing half of the visual field. Using such a compensatory eye-fixation pattern, they bisected the line almost correctly. There was no difference between the results with the hands used.

In contrast, the LVFD N(+) subjects showed no compensation for the hemianopia (fig. 1D). Once they fixated a certain point on the right part of the line, they persisted with this point and made a few rightward searches. At this point, they marked the subjective midpoint. Leftward searches never occurred. Taking the left homonymous hemianopia into account, it follows that they marked the subjective midpoint at the leftmost point of the line segment perceived in the seeing right visual field. Although the number of rightward searches and the time spent for line bisection varied among the

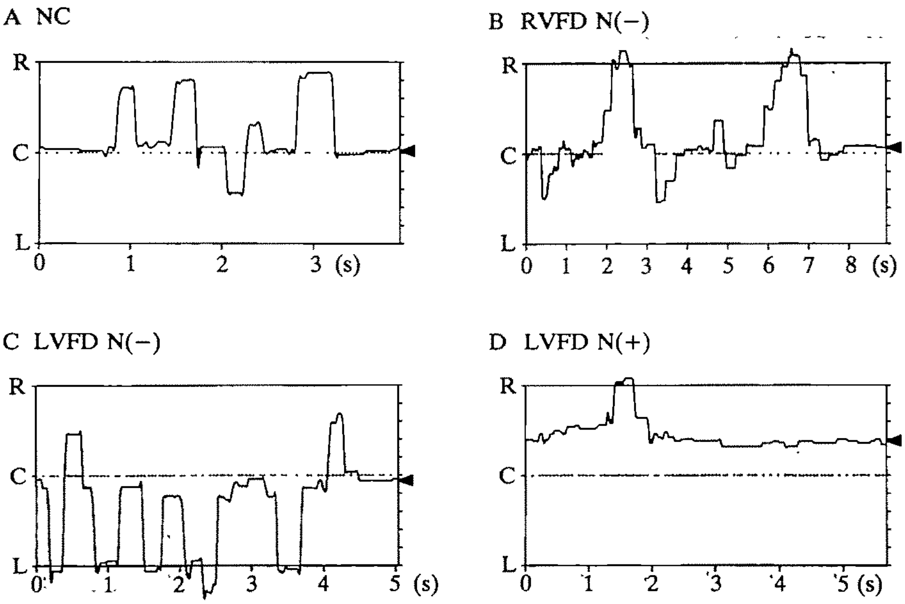


FIG. 1. Examples of the eye-fixation patterns in the line bisection test. R, C and L indicate the right endpoint, centre or true midpoint and left endpoint of the line, respectively. The arrowhead on the right indicates the subjective midpoint. The hemianopic side of the fixation graph is shadowed. NC = normal control.

subjects, this eye-fixation pattern was constantly observed in all the LVFD N(+) subjects.

Joanette *et al.* (1986) reported that patients with unilateral spatial neglect showed a better performance in the neglected field when manual pointing of visual stimuli was executed with the left hand than with the right. In our study, however, one patient with neglect who could use both hands showed no difference between the eye-fixation patterns with the right and left hands.

Effect of the line position and line length

The line bisection test was performed under the 3 hemispace conditions and the eye-fixation pattern was also recorded. The LVFD N(+) group of subjects were also tested with shorter lines (15 cm) under the same 3 conditions. There were thus 6 conditions for the LVFD N(+) subjects. Line bisection by the NC, RVFD N(−) and LVFD N(−) group subjects was correct under the 3 hemispace conditions. The eye-fixation pattern characteristic of each group was not influenced by the hemispace condition. The eye-fixation patterns under the 6 different conditions with regard to the line position and line length are shown for 2 LVFD N(+) cases in fig. 2. Case 1 constantly marked the subjective midpoint to the right of the true midpoint, irrespective of the line position or length. Case 7 placed the subjective midpoint near the true midpoint for the 15 cm lines under the 3 hemispace conditions and one 20 cm line under the right hemispace condition. Percentage deviation was calculated according to Schenkenberg *et al.* (1980), using the following formula.

$$\text{Percentage deviation} = \frac{\text{measured left half} - \text{true half}}{\text{true half}} \times 100 \quad .$$

Percentage deviations and actual deviations with means and SDs for the 6 line bisection conditions are listed for the LVFD N(+) group of subjects (Table 2). Each deviation value was measured in the trial used for the analysis of the eye-fixation pattern. The results of analysis of variance (ANOVA) applied to percentage deviations are also presented. Line position did not affect percentage deviation, although some patients showed better results under the right condition, as did Case 7. The subjects bisected 15 cm lines more correctly than 20 cm lines ($P < 0.05$; when ANOVA was applied to actual deviations, $P < 0.01$). In spite of the relatively exact bisection by some patients under certain conditions, the eye-fixation pattern characteristic of LVFD N(+) group appeared constantly. The subjects persisted with the point near the true midpoint and marked the subjective midpoint there. Leftward searches never occurred.

Quantitative analysis of directional searches

Quantitative analysis of directional searches was conducted for the bisection of 20 cm lines. The amount of rightward or leftward searches was investigated with reference to the subjective midpoint, which nearly corresponded to the baseline of the eye-fixation graph. On the eye-fixation pattern graphs, the areas between the subjective midpoint level and the eye-fixation pattern graph on the right were summed. The percentage of

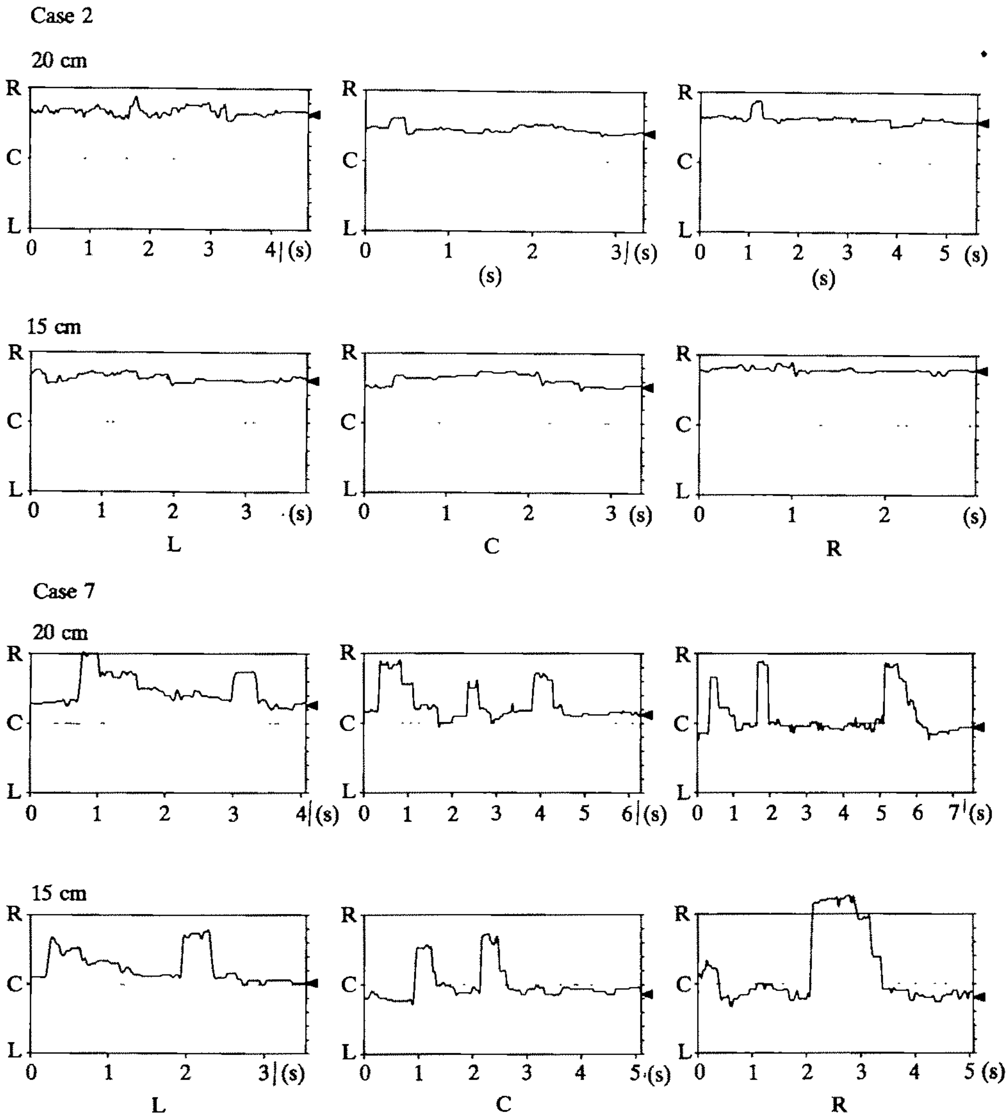


FIG. 2. Effects of line position and line length. L, C and R under the eye-fixation pattern graphs indicate three hemispace conditions, that is, the left hemispace, the centre and the right hemispace conditions, respectively. Case 1: the subjective midpoint was constantly marked to the right of the true midpoint, irrespective of line position or length. Case 7: the subjective midpoint was placed near the true midpoint in the cases of all three 15 cm and one 20 cm lines in the right hemispace. In both cases, the eye-fixation pattern characteristic of hemianopics with unilateral spatial neglect was constantly observed.

this total rightward search area relative to the half area of the graph box (percentage rightward search) was regarded as a measure of rightward searches (fig. 3). The percentage leftward search was obtained in the same way on the left from the subjective midpoint.

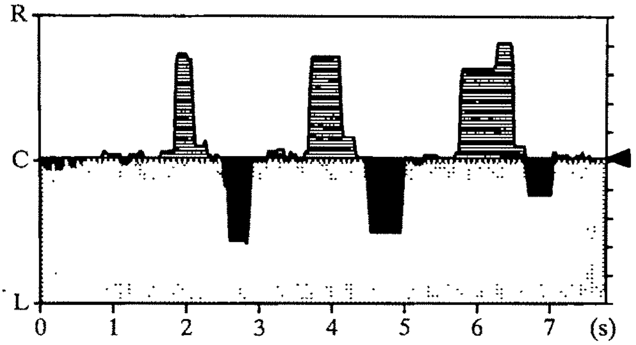
TABLE 2. PERCENTAGE AND ACTUAL DEVIATIONS OF THE SUBJECTIVE MIDPOINT MARKED BY THE LVFD N(+) SUBJECTS UNDER THE 6 LINE BISECTION CONDITIONS

	Percentage deviation with actual deviation (in cm) in brackets					
	20 cm			*15 cm*		
Case	*Left*	*Centre*	*Right*	*Left*	*Centre*	*Right*
1	60 (6.0)	72 (7.2)	68 (6.8)	62 (4.7)	52 (3.9)	72 (5.4)
2	64 (6.4)	40 (4.0)	58 (5.8)	60 (4.5)	52 (3.9)	78 (5.9)
3	38 (3.8)	34 (3.4)	40 (4.0)	16 (1.2)	26 (2.0)	4 (0.3)
4	42 (4.2)	32 (3.2)	36 (3.6)	14 (1.1)	18 (1.4)	−16 (−1.2)
5	26 (2.6)	36 (3.6)	30 (3.0)	−10 (−0.8)	4 (0.3)	2 (0.2)
6	16 (1.6)	20 (2.0)	18 (1.8)	−10 (−0.8)	−8 (−0.6)	−20 (−1.5)
7	26 (2.6)	16 (1.6)	−6 (−0.6)	2 (−0.2)	−14 (−1.1)	−20 (−1.5)
8	4 (0.4)	10 (1.0)	6 (0.6)	10 (0.8)	2 (0.2)	10 (0.8)
Mean	34.5 (3.45)	32.5 (3.25)	31.3 (3.13)	18.0 (1.35)	16.5 (1.24)	13.8 (1.03)
SD	20.7 (2.07)	19.1 (1.92)	25.0 (2.50)	28.3 (2.12)	25.4 (1.90)	39.5 (2.96)

Results of ANOVA applied to percentage deviation

Source	*Degrees of freedom*	*Sum of squares*	*F value*	*P value*
Line position	2	112.67	0.076	n.s.
Line length	1	3,333.33	4.518	<0.05
Interaction	2	4.67	0.003	n.s.
Error	42	30,989.0	–	–

Left = line in the left hemispace; Right = line in the right hemispace; Centre = line in front of the subject.



$$\text{Percentage rightward search} = \frac{\text{area } ▤}{\text{area } ⬚} \times 100$$

$$\text{Percentage leftward search} = \frac{\text{area } ■}{\text{area } ⬚} \times 100$$

FIG. 3. Quantitative analysis of directional searches. The fig. illustrates the method of quantifying searches in an example of the eye-fixation graph for a normal subject (20 cm line, centre condition). The extent of rightward or leftward searches was investigated with reference to the subjective midpoint, which corresponded approximately to the baseline of the eye fixation graph. This employed the percentage of the total right or left search area in relation to the half area of the graph box, indicated by the shaded frame in the lower section of the graph.

Effect of the line position and the hand used

One-way analysis of variance showed no differences in percentage rightward or leftward searches among the 3 line positions for the NC group of subjects with the right or left hands, or for the three hemianopic groups with the hand ipsilateral to the lesion (Table 3). The mean of the combined 3 line position data was therefore used for the following analysis. As for the NC group, there was no difference between percentage rightward searches with the right and left hands (df = 1,18, F = 0.20). The same was true for percentage leftward searches (df = 1,18, F = 0.82). Thus the mean of the combined right and left hand data was used for the NC group.

Rightward vs leftward searches

Fig. 4 shows the mean percentage rightward and leftward searches for each group. The mean percentage rightward search of the NC group was significantly higher than the mean percentage leftward search (Wilcoxon signed rank test, $P < 0.01$). This tendency to look to the right was found in all but one of the NC subjects who bisected the line with few movements of the eyes. The RVFD N(−) and LVFD N(−) group subjects showed more searches to the right and to the left, respectively ($P < 0.01$ and < 0.025). The search bias was directed to the hemianopic side in both hemianopic groups without unilateral spatial neglect. This directional bias was observed in all the subjects in the two groups. In the LVFD N(+) group of subjects, the mean percentage rightward search was significantly higher than the mean percentage leftward search ($P < 0.01$). The search bias was the opposite to that in the LVFD N(−) group subjects. The LVFD N(+) subjects rarely made leftward searches (mean percentage leftward search = 1.30, SD = 1.01), reflecting their characteristic eye-fixation pattern.

Intergroup analysis of percentage rightward and leftward searches

The four groups differed with respect to the mean percentage rightward and leftward searches (Kruskal-Wallis analysis of variance of ranks, H = 17.832, $P < 0.001$, and H = 19.835, $P < 0.001$). Intergroup analysis was therefore conducted by means of

TABLE 3. ANALYSIS OF PERCENTAGE RIGHTWARD AND LEFTWARD SEARCHES RELATED TO LINE POSITION

	Left hand		*Right hand*	
Percentage rightward search				
NC	df = 2,27	F = 0.91 n.s.	df = 2,27	F = 0.11 n.s.
RVFD N(−)	df = 2,21	F = 0.05 n.s.		–
LVFD N(−)		–	df = 2,12	F = 0.33 n.s.
LVFD N(+)		–	df = 2,21	F = 0.04 n.s.
Percentage leftward search				
NC	df = 2,27	F = 0.14 n.s.	df = 2,27	F = 0.48 n.s.
RVFD N(−)	df = 2,21	F = 0.18 n.s.		–
LVFD N(−)		–	df = 2,12	F = 0.55 n.s.
LVFD N(+)		–	df = 2,21	F = 0.89 n.s.

df = degrees of freedom; n.s. = nonsignificant.

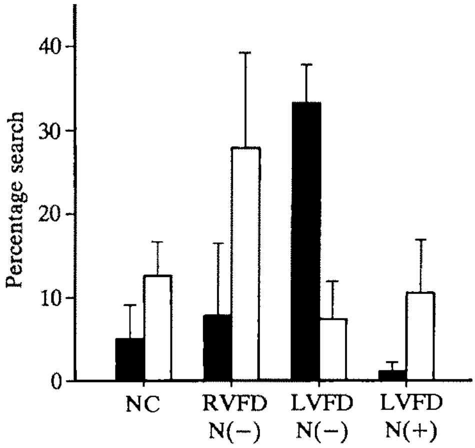


FIG. 4. Percentage rightward search (open bars) and percentage leftward search (solid bars) for each group. The mean values are shown, with 1 SD. Normal controls (NC) searched more to the right. Hemianopic patients without unilateral spatial neglect showed a larger mean percentage search to the hemianopic side. Hemianopics with unilateral spatial neglect rarely searched to the left.

a nonparametric equivalent of Williams' test (Shirley, 1977). The mean percentage rightward search of the RVFD N(−) group was significantly higher than those of the NC, LVFD N(−) and LVFD N(+) groups ($P < 0.01$ for all three groups), whose mean percentage rightward searches did not differ from one another. The LVFD N(−) group showed a significantly higher mean percentage leftward search than the NC, RVFD N(−) and LVFD N(+) groups ($P < 0.01$, < 0.05 and < 0.01, respectively). The LVFD N(+) group showed a significantly lower mean percentage leftward search than the NC, RVFD N(−) and LVFD N(−) groups ($P < 0.05$, < 0.01 and < 0.01, respectively).

Percentage total search

Hemianopic subjects without unilateral spatial neglect moved their fixation point more frequently and dynamically than the NC subjects, but those with unilateral spatial neglect showed an inactive eye-fixation pattern (fig. 1). The sum of percentage rightward and leftward searches (percentage total search) was used as a measure of the total search. The mean percentage total search was 17.66 for the NC group, 35.83 for the RVFD N(−) group, 40.66 for the LVFD N(−) group and 12.01 for the LVFD N(+) group. ANOVA showed the differences in the mean percentage total search among the four groups (df = 3,27, F = 22.30, $P < 0.001$). The RVFD N(−) and LVFD N(−) groups showed larger mean percentage total searches than the NC group ($P < 0.01$ and < 0.01). The LVFD N(+) group showed a smaller mean percentage total search than the RVFD N(−) and LVFD N(−) groups ($P < 0.01$ for both).

Time spent for line bisection (LB time)

Because the mean time spent for line bisection did not differ among the 3 hemispace conditions for each group, the average of the times under the 3 conditions was used for comparison. Moreover, for the NC group, there was no difference between the LB times using the right and left hands (paired-sample t test df = 9, t = 0.67). Thus the average of LB times with both hands was used for each NC subject. The mean LB time was 6.03 s for the NC group, 8.42 s for the RVFD N(−) group using the left hand, 6.82 s for the LVFD N(−) group using the right hand and 4.51 s for the LVFD N(+) group using the right hand. The four groups differed marginally with respect to the LB time (df = 3,27, F = 4.36, $P < 0.05$). The RVFD N(−) subjects required a significantly longer time than the subjects in the other three groups (df = 1,27, F = 9.24, $P < 0.01$). The LVFD N(+) subjects bisected the line in a significantly shorter time than the subjects in the other three groups (df = 1,27, F = 7.78, $P < 0.01$).

Right visual field of the LVFD N(+) subjects

After the line bisection test, the LVFD N(+) subjects were tested as to the ability to recognize the rightward deviation of their subjective midpoint in the seeing right half of the visual field. They were forced to keep fixating the left endpoint of the line and were asked about the adequacy of the subjective midpoint. One subject was not able to maintain fixation of the left endpoint of the line. All the remaining 7 LVFD N(+) subjects could appreciate the rightward deviation of the subjective midpoint in their right visual field. This result suggests that the right visual field of patients with unilateral spatial neglect has the visuospatial ability to estimate the true midpoint of the horizontal line.

DISCUSSION

Normal controls, hemianopic patients without unilateral spatial neglect and those with unilateral spatial neglect bisected lines with different visuospatial processing. Normal controls showed a tendency to look to the right in the line bisection test. This finding is in accord with the more powerful rightward than leftward orienting tendency in normals (Kinsbourne, 1970, 1987). However, considering that the line bisection test is for the most part a visuospatial task which partly involves analytical or metric factors, the rightward orienting tendency is expected to be reduced because of the right hemisphere activation by the task (Heilman and Watson, 1978). Such a relationship between eye movements and cerebral lateralization was supported by Kinsbourne's (1972) work which indicated that the direction in which people look while thinking reflects the lateralization of underlying cerebral activity. Studies on lateral eye movements (Gur *et al.*, 1975) also showed that right-handers move their eyes leftwards when solving spatial problems and rightwards for verbal problems. The right search bias in the line bisection test might be better explained on the basis of peripheral visual asymmetries. Beaumont (1985) recorded eye movements and examined the observation that right-handers prefer pictures with the important content to the right. He argued that lateral asymmetry in preferred picture arrangement was a consequence of gaze being directed to informative content on the right. This allowed more of the picture material to fall within the left visual field and be projected to the right hemisphere. He associated this fact with features of lateral neuropsychological dominance. Similarly, searching to the right to see most of the line in the left visual field might be more effective for exact line bisection, reflecting right hemisphere dominance for spatial tasks.

Normal controls scarcely searched to the right or left endpoint of the line. According to Posner (1980), in normal controls a peripheral visual stimulus summons attention covertly before and to some extent independently of any overt shifts, such as a change in eye position. While foveation improves the efficiency of processing visual events in terms of increased acuity, directing attention covertly to a visual location improves the speed. Thus normal controls were considered to direct their attention to both endpoints of the line with partly covert and partly overt orientings.

Left hemianopics without unilateral spatial neglect searched to the left endpoint of the line, overcoming the right search bias observed in normal controls, and bisected the line correctly. Because of the left homonymous hemianopia, covert orienting of attention was not possible towards the left side of the fixation point. They had to shift their gaze to see the left endpoint of the line. As for the right endpoint, combined covert and overt orienting of attention could be employed as in normal controls. Conversely, right hemianopics without unilateral spatial neglect could not direct their attention to the right covertly. Thus rightward searches had to reach the right endpoint of the line, resulting in the exaggerated rightward bias of searches as compared with that in normal controls. In hemianopic patients without unilateral spatial neglect, covert and overt orienting of attention was considered to occur effectively in addition to compensation for visual field defects.

In the case of left hemianopics with unilateral spatial neglect, the amount of searches to the right, that is, to the side of the normal field, was almost the same as that in normal controls. However, they showed no searches to the left. This asymmetry of the directional searches can be explained by any of the following hypotheses: attentional imbalance (Kinsbourne, 1970, 1987), right hemisphere dominance for attention (Heilman and Van Den Abell, 1980; Weintraub and Mesulam, 1987) and directional hypokinesia (Heilman and Valenstein, 1979; Heilman *et al.*, 1983*a*, 1987). The relationship that we observed between the subjective midpoint and the line segment perceived in the seeing right visual field contradicted the expected results. Left hemianopics with unilateral spatial neglect neither marked at the centre of the perceived line segment nor placed the mark to the right of the centre, neglecting the left part of this segment. Instead, they placed the subjective midpoint on the leftmost point of this segment. This unexpected result cannot be explained by the above hypotheses. That the patients understood the meaning of line bisection was established by the fact that they could appreciate the rightward deviation of the subjective midpoint in the seeing right visual field. There must therefore be some reason for them to judge such a point on the line as the midpoint.

Critchley (1950) pointed out that unawareness of homonymous hemianopia is not infrequent. Gassel and Williams (1963) stated that the hemianopic field is an area of absence which is discovered rather than sensed. In our study, 6 of 8 left hemianopics with unilateral spatial neglect showed total unawareness of the defect and the remaining 2 complained of blurring in the left eye. However, Bisiach *et al.* (1986) found a clear double dissociation between anosognosia for visual field defects and hemineglect. It is difficult therefore to explain the relationship between the subjective midpoint and the line segment perceived in the right field only by unawareness of the hemianopia. Here we need to consider the meaning of the inner representation of visual stimuli in the left visual half field, which is objectively characterized as a blind area.

The fact that visual forms were completed across blind sections of the visual field in patients with hemianopia was discovered by Poppelreuter (1917). Fuchs (1920) claimed that the effect could be elicited only with simple, regular and symmetric figures. Meaningful drawings, letters, words, straight lines and homogeneous surfaces were never completed. Kinsbourne and Warrington (1962), however, reported paralexic errors predominantly limited to the beginning of the word in patients with right hemisphere disease, and considered this type of paralexia as word completion. Warrington (1965) concluded that completion responses were most readily given to those forms with which the patient was familiar and which would be expected to be seen in complete form. Warrington (1962) found this tendency of completion to be strongly associated with the presence of a parietal lobe lesion of either hemisphere, as well as with the symptom of unawareness of the field defect. She also demonstrated a trend for completion to be associated with unilateral neglect.

Although completion of a line has not been reported, we have interpreted our results by applying the concept of completion to unilateral spatial neglect on the line bisection test. Left hemianopic patients with unilateral spatial neglect see a completed image of a line extending equally to either side of the point where they are going to mark the subjective midpoint. The completed line has a length twice that of the perceived one in the seeing right visual field (fig. 5A). Thus the patients regard the leftmost point of the line segment actually perceived in the right visual field as the midpoint. The completed line corresponds to the represented line determined on the basis of the midpoints set by the patients on the objective lines (Bisiach *et al.*, 1983). In contrast, if the patients are compelled to fixate the left endpoint of the line and see the whole line in the seeing right field, completion never occurs (fig. 5B).

Gassel and Williams (1963) pointed out that the error of completion was most resistant to demonstration in those patients in whom the direction of attention was unsuccessful. Our results showed that the eye-fixation patterns of left hemianopics with unilateral spatial neglect were static, with no leftward searches. Thus they were considered to exhibit a tendency to completion during free viewing of objects. Warrington (1962) showed that completion was not limited to brief exposure but that it still occurred in many cases with exposures lasting up to 1.5 s. These cases might be patients with poor movements of the fixation point and attention. Recently, Sergent (1988) suggested that reports of perceptual completion were determined by many factors, not all related to seeing more than what was objectively available. One of these factors, eccentric fixation towards the hemianopic field, was found in her patients irrespective of unilateral spatial neglect. However, such eccentric fixation was not considered to be involved in the line bisection test, because left hemianopics with unilateral spatial neglect showed no movement of the fixation point towards the hemianopic field.

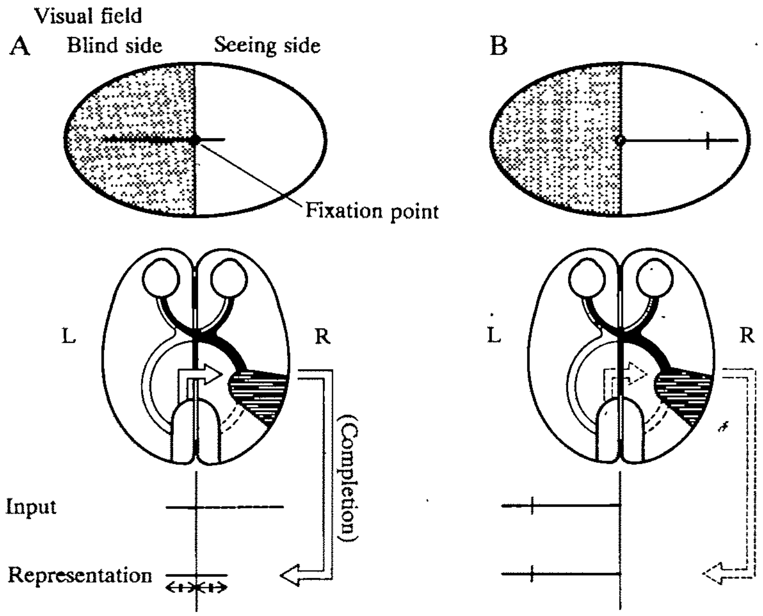


FIG. 5. A, scheme for the mechanism underlying unilateral spatial neglect in the line bisection test. B, recognition of the rightward deviation of the subjective midpoint in the seeing right visual field. The patient is forced to maintain fixation of the left endpoint of the line.

P. A. Reuter-Lorenz, M. Moscovitch and M. Kinsbourne (personal communication) found a neglect-like phenomenon in the visual half field of normals by the use of a tachistoscopic line bisection judgement. Our results showed, however, that the left hemisphere could appreciate the deviation of the subjective midpoint through the right visual field. Studies on split-brain patients and right hemisphere-damaged patients have revealed the visuospatial ability of the left hemisphere (LeDoux *et al.*, 1977, 1980; Zaidel *et al.*, 1981). As stated by LeDoux *et al.* (1980), it seems acceptable to attribute the visuospatial disorders in free vision to pathological changes in the right hemisphere. Accordingly, the mechanism underlying unilateral spatial neglect on the line bisection test can be explained as follows (fig. 5A). Visual input about the right part of the line is projected to the left hemisphere from the right visual field. The damaged right hemisphere uses the visual input, probably via the corpus callosum, and constructs a totalized image of the line extending equally to either side of the fixation point. As a result, left hemianopics with unilateral spatial neglect judge the point which they have persisted to fixate as the midpoint and stop further searching. The strong tendency to construct a totalized image inhibits the visuospatial ability of the left hemisphere. Such interactions between the hemispheres were considered to play an important role in unilateral spatial neglect. As the cause of attentional bias, Kinsbourne (1970) emphasized the loss of inhibition of the intact hemisphere by the injured one. He proposed that transection of the corpus callosum in cases of neglect would therefore be therapeutic. Contrary to this report, we considered that the lesioned right hemisphere would inhibit or interfere with the ability of the intact left hemisphere. Crowne *et al.* (1981) and Watson *et al.* (1984) reported that callosal section led to the reappearance of neglect in monkeys with lesions of the frontal eye fields that had recovered from neglect. Recently, Kinsbourne (1987) himself agreed with this view and stressed the role of intercollicular commissures in the balance of attention. However, the effect of callosal section on parietal neglect in man has not been reported and Kinsbourne's (1970) proposal is still attractive. If visual input, visuospatial judgement and motor output are all processed in the left hemisphere, unilateral spatial neglect is expected to improve at least in the line bisection test. Otherwise, left hemianopics with unilateral spatial neglect may bisect the line segment perceived in the seeing right visual field.

In this study, only patients with homonymous hemianopia were included, because we could not examine neglect patients whose visual field contralateral to the lesion was shown to be completely normal by perimetry. Another reason was that a perimetrically normal field is not necessarily intact in cases with hemisphere lesions (De Renzi, 1982). However, we were able to record the eye-fixation pattern of a neglect patient with a parietal lesion who was not hemianopic on confrontation testing and showed extinction on double simultaneous visual stimulation. The eye-fixation pattern in this patient was the same as that of hemianopics with unilateral spatial neglect. In the line bisection test, patients without hemianopia but with extinction also cannot shift their attention to the left endpoint of the line while seeing the right endpoint in the right visual field. Thus the hypothesized mechanism would also be applicable to this patient's neglect in the line bisection test.

All our patients had lesions in the right parietal lobe. Although unilateral spatial neglect commonly occurs following right parietal lesions (Critchley, 1953; De Renzi, 1982; Heilman *et al.*, 1983*b*; Vallar and Perani, 1987), it may result from left hemisphere disease (Battersby *et al.*, 1956; Gainotti *et al.*, 1972; Zarit and Kahn, 1974; Ogden, 1987) or lesions at other sites (Heilman and Valenstein, 1972; Watson *et al.*, 1973, 1981; Ferro and Kertesz, 1984; Vallar and Perani, 1987). Gainotti *et al.* (1986) suggested that there may be different mechanisms for unilateral spatial neglect in relation to laterality of cerebral lesions. As for lesion sites, Posner *et al.* (1984) reported that the effects of brain injury on disengagement of attention seem to be unique to the parietal lobe. There may be different mechanisms for the neglect due to frontal, cingulate and thalamic lesions, as suggested by Mesulam (1981). Further investigation is therefore needed on such cases of neglect.

There remain two other possible explanations for the observation that hemianopics with unilateral spatial neglect marked the subjective midpoint on the leftmost point of the line segment perceived in the right visual field. The first is that they had been trained to mark the subjective midpoint on the left extreme of the perceived line segment in order to lessen the rightward deviation. This explanation is unlikely, because rehabilitation had not been started in Cases 1, 3 and 4 at the time of examination. The second is that, because of the reduced arousal or activation after a right hemisphere stroke (Heilman *et al.*, 1978; Heilman and Van Den Abell, 1979; Coslett *et al.*, 1987), the patients carelessly place the subjective midpoint at the point they are looking at, probably with tacit awareness of the line extending to the left side. However, it seems improbable that carelessness is the primary cause of the abnormal marking behaviour, because the amount of their rightward searches was almost the same as that of normal controls.

Hemispace is of importance in determining the symptoms of unilateral spatial neglect (Heilman and Valenstein, 1979; Bowers and Heilman, 1980). However, the results showed that hemispace did not affect the visuospatial process represented by the eye-fixation pattern in the line bisection test. Even if the subjective midpoint was placed on the true midpoint or to the left of it, the eye-fixation pattern characteristic of hemianopics with unilateral spatial neglect was constantly observed. Thus unilateral spatial neglect cannot be excluded by the absence of rightward deviation in the line bisection test. We found diverse patterns as to the relationship between the subjective midpoint and the line position or length, as Bisiach *et al.* (1983) reported. In some patients, fixation was magnetized to the right endpoint, independently of the line position, while in others fixation tended to be confined to a certain place of the outer space governed by the body midline. Further study is needed on the problem as to what determines the point on the line at which left hemianopic patients with unilateral spatial neglect persist in fixating.

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NONVERBAL RECOGNITION AND RECENCY DISCRIMINATION DEFICITS IN PARKINSON'S DISEASE AND ALZHEIMER'S DISEASE

by E. V. SULLIVAN *and* H. J. SAGAR[1]

(From the Department of Brain and Cognitive Sciences and Clinical Research Center, Massachusetts Institute of Technology, Cambridge, Massachusetts, and Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA)

SUMMARY

In a study of verbal temporal ordering, patients with Parkinson's disease (PD) were impaired in making judgements of the relative recency of serially-presented words but were normal in word recognition; by contrast, patients with Alzheimer's disease (AD) were impaired on both verbal tasks (Sagar *et al.*, 1985, 1988*b*). The present study used a nonverbal analogue of the verbal temporal ordering task to examine whether the deficit in recency discrimination of the PD patients transcended material-specific bounds or was specific to verbal material. The nonverbal task was administered to the patients with PD, patients with AD and normal control subjects studied with the verbal task. The results showed that the retention functions for the recognition of verbal and nonverbal material differed qualitatively from each other and this difference was present in all three subject groups. For verbal and nonverbal recency discrimination and verbal content recognition, performance declined with increasing retention intervals; for nonverbal content recognition, however, performance was essentially unchanging across retention intervals. As on the verbal test, recency discrimination on the nonverbal test was impaired in both patient groups. In contrast to the results with the verbal task, both groups were impaired on content recognition. The patterns of impairment, however, differed between the two patient groups in a parallel way to those of the verbal task: performance of the AD group was impaired at the longest retention intervals but not at the shortest intervals, whereas the performance of the PD group was impaired at the shortest but not at the longest intervals. This deficit in nonverbal short-term recognition memory was present even in PD patients who scored within the normal range on a quantitative test of dementia. These results show that deficits in recency discrimination and short-term memory processing in PD extend to nonverbal as well as verbal material and imply bilateral frontal lobe dysfunction in the genesis of these deficits.

INTRODUCTION

In a study of verbal temporal ordering, patients with Parkinson's disease (PD) were observed to have impaired recency discrimination but spared word recognition, whereas patients with Alzheimer's disease (AD) were impaired on both tasks (Sagar *et al.*, 1985, 1988*b*). Furthermore, patients with PD but not AD showed evidence of bradyphrenia, in that the PD patients' recognition of the most recently presented words was poorer than that of later occurring words. These results indicated that bradyphrenia and impaired

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Correspondence to: Dr E. V. Sullivan, Psychiatry Service (116A3), Veterans Administration Medical Center, Palo Alto, CA 94304, USA.

[1] Present address: Department of Neurology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK.

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temporal discrimination are selective deficits of PD and were interpreted as impairments in short-term memory and use of temporal order.

The pattern of impaired recency discrimination with spared content recognition was first documented in patients with lesions confined to the frontal lobes (Milner, 1971, 1982; Corsi, 1972). The recency discrimination deficit tended to be material specific; recency discrimination of nonverbal material was impaired following right, but not left, frontal lesions, whereas recency discrimination of verbal material was impaired by lesions on either side, although more severely after left-sided than right-sided lesions. The results of that study showed dissociations between verbal and nonverbal performance depending on the site of the pathology and, taken with the results of our earlier study, suggest that the verbal recency discrimination deficit of PD may be indicative of either left or bilateral frontal lobe dysfunction. Although motor symptoms of PD can be asymmetric, positron emission tomography studies (Garnett *et al.*, 1984; Kuhl *et al.*, 1984) reveal bilateral cortical involvement, even in PD patients with clinically unilateral symptoms. It remains unknown, however, whether the bilateral frontal lobe pathology in PD produces cognitive signs of bilateral disease. Accordingly, we looked for material specificity of recency discrimination in PD by administering a nonverbal recency task to subjects who had taken the analogous verbal task. In addition, we sought to observe a short-term memory deficit in PD as was observed in the verbal task.

METHODS

Subjects

The subjects were 14 patients with PD, 15 patients with AD, and 15 healthy control subjects (Table 1). All subjects had participated in the verbal study; only 1 subject from the verbal study (a man with PD) was not available to participate in the nonverbal study. The patients were drawn from the Memory Disorders Unit and the Movement Disorders Unit at the Massachusetts General Hospital. The diagnosis of AD was based on strict inclusion and exclusion criteria (McKhann *et al.*, 1984; Khachaturian, 1985). The diagnosis of PD was based on the presence of two of the three cardinal signs of akinesia, rigidity and extrapyramidal rest tremor. All patients were ambulant and free from psychiatric disease. All PD patients were treated with antiparkinsonian medication, in the majority of cases a levodopa preparation combined with carbidopa, and responded favourably. Hoehn and Yahr's (1967) ratings of the PD patients ranged from stages 2 to 4 for 13 patients; 1 PD patient was in stage 1 at the time of testing and showed

TABLE 1. CHARACTERISTICS OF SUBJECT GROUPS: MEANS AND RANGES

Group	*Age (yrs)*	*Education (yrs)*	*Duration of disease (yrs)*	*Blessed Dementia Scale Score (max. = 37)*
Control (7M, 8F)	63.1 (54–77)	13.7 (10–19)	Not applicable	0.3 (0–2)
Parkinsonian (12M, 2F)	64.1 (52–80)	15.4 (8–20)	5.9 (1–13)	3.3 (0–12)
Alzheimer (7M, 8F)	63.5 (53–76)	14.9 (12–20)	3.2 (2–7)	8.6 (5–16)

M = male; F = female.

left-sided signs, which progressed to be bilateral. Neither patient group was treated with any primarily psychoactive medication. Patients were not selected for study on the basis of behavioural criteria or treatment regime. The groups were matched for age and years of education but the PD group had a higher male-to-female sex ratio than the other two groups. The PD group had a longer mean duration of illness but was less demented as judged by performance on the memory and orientation section of the Blessed Dementia Scale (BDS) (Blessed *et al.*, 1968), which provides a quantitative measure of severity of dementia.

Informed consent for neuropsychological testing was obtained from all subjects.

Procedure

This test followed an identical procedure to the verbal version (Sagar *et al.*, 1985, 1988*b*) but used as stimuli abstract wallpaper designs mounted on 5×8 inch cards. Designs were selected that could not easily be labelled verbally. Subjects sat opposite the examiner and were presented with a series of 493 cards at a rate of about 1/2 s. They were instructed to look carefully at the designs and to remember them in their order of appearance. Responses were recorded by hand by the examiner.

At random intervals throughout the series, one of two questions appeared on a card and was read by the examiner. 'Which of these have you seen in this test?' was followed by a content recognition test in which a previously presented design and a foil were shown side by side on a single card. 'Which of these did you see more recently?' was followed by a recency discrimination test in which 2 previously presented designs were displayed on one card. Subjects had unlimited time to point to their answer. In these two-choice tests, 50% of the correct responses appeared on the left side of the card and 50% on the right in random order.

Test questions occurred at varying intervals after stimulus presentation. A stimulus-test interval was defined as the number of intervals between events where an event was either another stimulus design or a test question. For example, where a question immediately followed stimulus presentation, the stimulus-test interval was 1 and there were no intervening events. The position of a content recognition question was defined by one such interval. Recency discrimination questions examined 2 previously presented designs; the position of a recency discrimination question, therefore, was defined by two intervals, one corresponding to each design examined.

For content recognition, the stimulus-test intervals were 1, 3, 6, 10, 15, 25, 50, 100, and 150, with 5 tests at each interval. For recency discrimination, all possible pairings of these stimulus-test intervals were used (1−3, 1−6, 1−10, . . . , 50−100, 50−150, 100−150), with 5 tests for each pairing.

Statistical analysis

The analysis of the nonverbal test followed exactly the approach used for the verbal test and the description is the same (Sagar *et al.*, 1988*b*). Specifically, results were calculated separately for content recognition and recency discrimination as the mean percentage correct at each stimulus-test interval. For recency discrimination in some analyses, results were pooled for each position of the more recent stimulus and performance was assessed across stimulus-test intervals corresponding to the more recent stimuli of the pair. Other analyses examined the effect on performance of increasing interstimulus intervals: for each position of the recent stimulus, the results were analysed according to the position of the more remote stimulus. Total percentage correct was the mean of the average performances at each stimulus-test interval.

Analyses of variance (ANOVA) of group by task (content or recency) by interval were performed. Arcsin square root transformations were used to produce normal distributions of data with homogeneous variances. All stimulus-test intervals were examined separately in the 3-way ANOVA. When ANOVA yielded significant differences among data sets, planned paired comparisons were performed using Fisher tests and t tests (2-tailed). In order to reduce the number of possible comparisons, planned tests were performed on data from pooled interval triads (i.e., 1+3+6 vs 10+15+25 vs 50+100+150). As had been done for the verbal test, results in graphic representations were pooled for intervals beyond the theoretical limit of short-term memory (i.e., intervals greater than 6) as 10, 15, 25 and 50, 100, 150 so as to eliminate irregularities in the forgetting curve that may have resulted from reduced numbers of data points at longer intervals. Correlations were based on Pearson product-moment tests.

RESULTS

Total scores

For all groups, recency discrimination was more difficult than content recognition (3-way ANOVA, $F(1,41) = 176.58$, $P < 0.001$). Significant differences emerged among groups, however, in their performance on content recognition and recency discrimination ($F(2,41) = 7.22$, $P < 0.003$); relative to control subjects, both patient groups were impaired in content recognition (1-way ANOVA, $F(2,41) = 4.827$, $P < 0.02$ and Fisher tests) and recency discrimination (1-way ANOVA, $F(2,41) = 7.847$, $P < 0.002$ and Fisher tests) and did not differ from each other. Total content and recency scores were correlated in the healthy control ($r = 0.591$, $P < 0.025$) and PD groups ($r = 0.603$, $P < 0.025$), but not in the AD group ($r = 0.06$). The group-by-task interaction was not significant.

Effect of stimulus-test interval

For all groups, performance declined with increasing stimulus-test interval (Table 2, fig. 1) ($F(7,287) = 3.38$, $P < 0.002$). The task-by-interval interaction was highly significant ($F(7,287) = 6.85$, $P < 0.001$). Fig. 1 shows that, for all groups, the content recognition function is nearly flat, whereas recency discrimination declined with increasing stimulus-test interval.

The groups differed in the relationship between test performance and stimulus-test interval, as indicated by the significant group-by-interval interaction ($F(14,287) = 1.79$, $P < 0.05$). Mean scores for each interval are shown in Table 2 and for pooled intervals in fig. 1. For recency discrimination, the performance of AD and PD patients was inferior to that of normal control subjects. The relationship between performance and stimulus-test interval did not, however, differ between the two patient groups. For content recognition, by contrast, the PD and AD groups showed qualitatively different patterns of performance:

TABLE 2. TOTAL SCORES AT EACH STIMULUS-TEST INTERVAL*

	Stimulus-test intervals									
Condition	*1*	*3*	*6*	*10*	*15*	*25*	*50*	*100*	*150*	*Total*
Content										
Control	80	73.3	80	92	74.7	85.3	82.7	80	72	80
	5.2	6.1	5.5	3.3	3.1	4.6	4.3	4.8	3.8	2.5
Parkinsonian	58.6	58.6	68.6	81.4	74.3	77.1	75.7	84.3	58.6	70.8
	4.4	7	6.9	5.7	6.1	5.5	7.6	5.2	6.1	3.1
Alzheimer	64	61.3	78.7	72	72	82.7	69.3	68	57.3	69.3
	6.5	5.7	4.6	4.7	4.7	4.7	5.8	5.1	5.5	1.9
Recency										
Control	79.9	61	64.6	62.7	61.5	71	48.7	53.3	–	62.5
	2.6	2.2	2.5	3.1	3.3	2.9	3.5	5	–	1.6
Parkinsonian	68.3	55.2	58.1	55.7	59.3	56.2	47.9	57.1	–	56.8
	4.5	1.8	2.4	3.7	4.2	5	3.9	5.4	–	2
Alzheimer	62	54.2	49.5	54.4	45.3	58.7	45.3	56	–	52.9
	4.5	2	2.5	2.6	3.6	3.2	3.4	6.2	–	1.4

* Upper figures = mean percentage correct; lower figures = SEM.

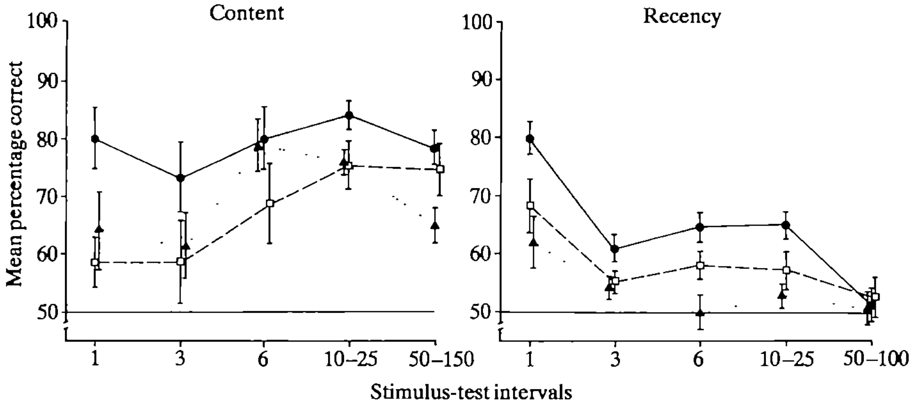

FIG. 1. Test performance related to the interval between stimulus and test (mean and ± 1 SEM). Control (● – ●); parkinsonian (□–□); Alzheimer (▲···▲).

the PD group was impaired at the shortest pooled stimulus-test interval, i.e., 1+3+6 (1-way ANOVA, F(2,41) = 4.384, $P < 0.02$ and Fisher tests), but not at the two longer pooled intervals, i.e., 10+15+25 and 50+100+150, whereas the AD group was impaired only at the longest pooled interval (1-way ANOVA for 10+15+25, F(2,41) = 2.471, $P < 0.10$; for 50+100+150, F(2,41) = 3.644, $P < 0.035$ and Fisher tests).

Effect of severity of dementia

In order to examine the effects on performance of severity of dementia, the groups were divided according to their scores on the memory and orientation section of the BDS on which normal control subjects scored a maximum of 2. The PD group was divided into Group 1 with normal BDS scores (0–2) and Group 2 with abnormal BDS scores (3–12). The AD group was divided into a mildly demented subgroup that matched the PD Group 2 for BDS scores (3–12) and a moderately demented subgroup (BDS > 12) for which no parallel existed among the PD patients.

Neither total content recognition nor total recency discrimination differed between Group 1 patients and normal control subjects, or between PD Group 2 patients and mildly demented AD patients (fig. 2). Inspection of fig. 2, however, reveals two findings of special interest: first, despite the absence of difference on total content scores, PD Group 1 was significantly worse than the control group at the stimulus-test interval of 1 (t(20) = 2.276, $P < 0.035$); secondly, content recognition of PD Group 2 was more akin to the moderately demented AD group than to the matched AD group with mild dementia.

The relationship between total scores and severity of dementia was similar in the two patient groups for content recognition but differed for recency discrimination. For content recognition, the correlations between test score and BDS were not significant in either group (for PD, r = 0.29; for AD, r = 0.03). For recency discrimination, however, PD patients with higher BDS scores achieved significantly lower scores (r = –0.71,

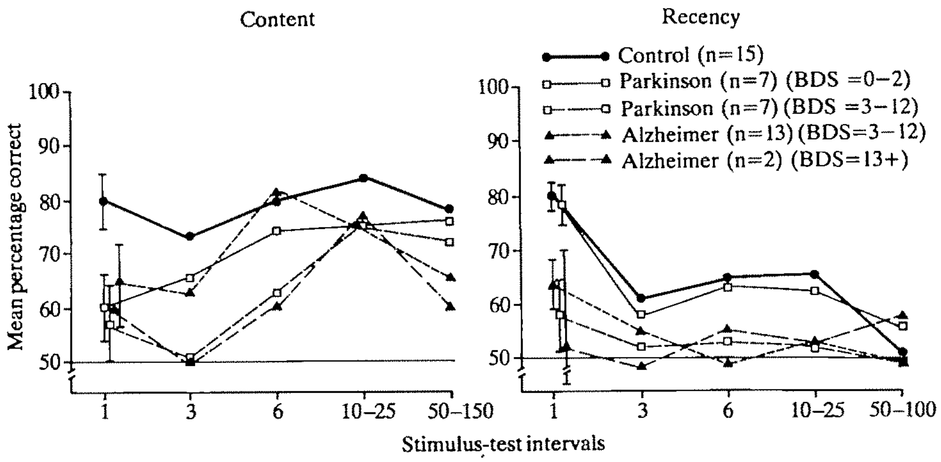

FIG. 2. Test performance across stimulus-test intervals related to dementia rating (mean and ±1 SEM).

$P < 0.01$). In AD, the correlation between recency discrimination performance and BDS was not significant (r = 0.35).

Relationship between the verbal and nonverbal tests

Subjects of this study also participated in the assessment of *verbal* content recognition and recency discrimination by Sagar *et al.* (1988*b*). The relationship between verbal and nonverbal performance could, therefore, be assessed within subjects by comparison of results from parallel tests. For content recognition and recency discrimination, total scores on the verbal and nonverbal tests were compared within groups using correlations. For *content* recognition, scores on the verbal test were not good predictors of scores on the nonverbal test for any group (PD: r = 0.28; AD: r = 0.17; healthy control: r = 0.31). For *recency* discrimination, by contrast, the correlation between the verbal and nonverbal scores was significant for the PD patients but not for the AD patients or healthy control subjects (PD: r = 0.64, $P < 0.015$; AD: r = 0.11; healthy control: r = 0.45, $P = 0.093$). The correlations suggest that verbal and nonverbal recency discrimination was affected to parallel degrees in the PD patients, but not in the AD patients or healthy control subjects.

The task-by-interval interaction was significant on the nonverbal test but not on the verbal test (Sagar *et al.*, 1988*b*). This difference between the verbal and nonverbal forms of the tests shows that content recognition and recency discrimination have different relationships to stimulus-test interval in the nonverbal test but have similar relationships to stimulus-test interval in the verbal test; in the nonverbal test, recency discrimination declined with increasing stimulus-test intervals but content recognition remained stable regardless of interval length. Fig. 3 shows that, even within the normal control group, verbal content recognition declined with increasing stimulus-test interval whereas nonverbal content recognition did not.

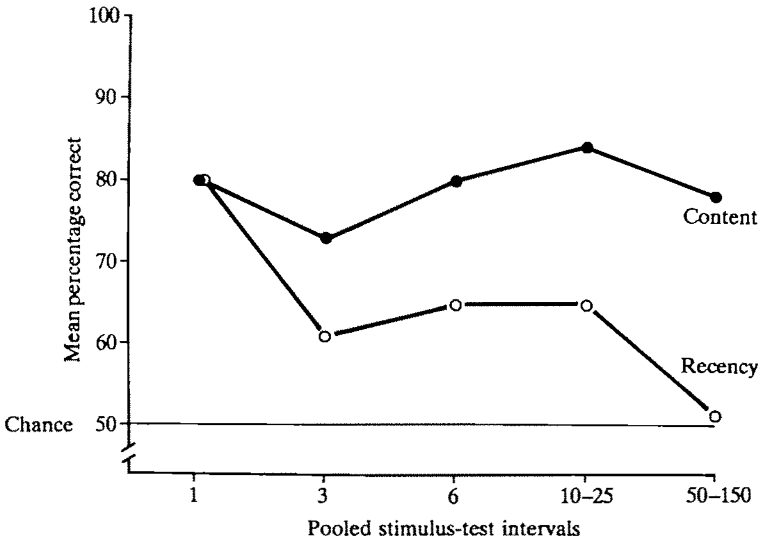

FIG. 3. Content recognition and recency discrimination mean scores of the normal control group (n = 15) related to stimulus-test interval.

In considering the possibility that the 1 PD patient with unilateral left-sided motor signs would perform better on the verbal than on the nonverbal test, his scores were viewed separately (Table 3). His total content and recency scores for the verbal test were nearly the same as those for the nonverbal test; if any difference existed, it favoured nonverbal material. This result suggests that at the time of testing the patient showed cognitive but not motor signs of bilateral pathology. This dissociation probably reflects the greater sensitivity of cognitive function to the effects of underlying bilateral pathology but could indicate dissociations among the subcorticocortical circuits affected early in the disease. At clinical assessment, 2.5 years later, this patient showed bilateral motor signs.

Despite the involvement of both nonverbal and verbal processes in this patient, some evidence for disproportionate effects on nonverbal performance was shown when results were analysed according to stimulus-test interval (Table 3): impairment at the stimulus-test

TABLE 3 SCORES ON THE VERBAL (VTO) AND NONVERBAL (NVTO) TEMPORAL ORDERING TESTS OF A PD PATIENT WITH UNILATERAL LEFT-SIDED MOTOR SIGNS

Test and condition	*Stimulus-test intervals*					
	1	*3*	*6*	*10–25*	*50–150*	*Total*
VTO						
Content	100	80	100	66.7	60	73.3
Recency	90	69	67	52.7	30	55.5
NVTO						
Content	40	80	80	86.7	73.3	75.6
Recency	73	57	57	59.7	45	57

interval of 1, reflecting a deficit in short-term memory, was seen for nonverbal, but not verbal material, in keeping with the clinical evidence of greater right cortical and subcortical pathological involvement.

DISCUSSION

The results of this study showed that, first, recency discrimination and recognition memory for nonverbal material were impaired in PD and AD; secondly, the pattern of impairment differed with aetiology; and thirdly, the recognition of verbal and nonverbal material differed qualitatively from each other in the normal control group as well as the patients groups. Each result is discussed in turn.

Impaired recency discrimination in PD and AD

In the present study, the PD and AD patients were impaired in nonverbal recency discrimination as they were in the verbal task (Sagar *et al.*, 1985, 1988*b*). Taken together with the observations from studies of unilateral frontal lobe excision (Milner, 1971, 1982; Corsi, 1972), these results suggest that frontal lobe dysfunction in PD and AD occurs bilaterally. In this study, virtually all PD patients had bilateral motor deficits and only for the PD group were scores on the verbal test significantly correlated with scores on the nonverbal test. Even in the clinically unilateral case of PD, the deficit was present for both verbal and nonverbal material. Thus the study demonstrates cognitive deficits of bilateral frontal lobe dysfunction in PD even when motor signs are unilateral. The cognitive findings in pure hemiparkinsonism, however, require confirmation in a larger group of patients.

One possible explanation of defective recency judgement is that it occurs as a consequence of a deficit in content memory (Squire *et al.*, 1981). Although in this study, impaired nonverbal recency discrimination could be a simple consequence of attenuated content memory, we believe this to be unlikely for the following reasons. First, content recognition and recency discrimination are dissociable (Milner, 1971, 1982). The most relevant recent example is the study of the amnesic patient H.M. (Scoville and Milner, 1957; Corkin, 1984), who showed spared capacity for recency judgement despite impaired content memory on our tests of verbal and nonverbal temporal ordering (Sagar *et al.*, 1984). Secondly, the results of the present study support those of the verbal study (Sagar *et al.*, 1988*b*) in which recency discrimination was disproportionately impaired in PD. Thirdly, in a study of amnesic patients of differing aetiology, impairment in temporal order judgement was significantly greater in patients with frontal lobe disorder (Shimamura *et al.*, 1989). As applied to the present study, these findings suggest that the content and recency results in PD and AD represent deficits in separate cognitive systems. This interpretation is supported further by the absence of correlation between content and recency performance in the AD group.

Evidence converging from this and related studies suggests that a recency discrimination deficit is specific to PD and not necessarily attributable to general cognitive decline associated with Alzheimer-type dementia. On the verbal task, the group by task interaction was significant, indicating a disproportionate deficit in recency discrimination in PD (Sagar *et al.*, 1988*b*). Although this interaction was not significant on the nonverbal task, other similarities between the two tests indicate that nonverbal recency discrimination may also be a specific deficit in PD; the lack of group-by-task interaction may be due to a floor effect in the total scores of nonverbal recency discrimination. First, for both the verbal and nonverbal temporal ordering tests, the PD group, but not the AD group, showed a significant relationship between high dementia ratings and poor recency discrimination, suggesting that deficient recency discrimination is a feature of advancing parkinsonian dementia but not necessarily of Alzheimer-type dementia. Secondly, verbal and nonverbal recency test performance was related in PD but not AD, whereas verbal and nonverbal content recognition were not correlated in either disease. The significant correlation in recency discrimination in the PD group also implies bilateral involvement of this frontal lobe function.

Impaired recognition of nonverbal material in PD and AD

Although both patient groups were impaired on nonverbal content recognition, they showed different patterns of impairment, in that the recognition scores of the PD group were impaired at the shortest but not at the longest intervals whereas the scores of the AD group were impaired at the longest but not at the shortest intervals. Nonverbal recognition deficits are well-established in AD (e.g., Corkin *et al.*, 1981, 1986; Corkin, 1982), but previous studies of PD have reported impairment in recall but not recognition of nonverbal visual material (Flowers *et al.*, 1984). In the present study, the nonverbal recognition deficit was limited to short-term memory. The study by Flowers *et al.*, however, tested recognition at a minimum of 1 min, after which stimulus presentation in our study fell within the time frame of long-term memory, for which PD patients performed normally. Flowers *et al.* may thus have failed to find a nonverbal recognition deficit because short-term memory was not specifically examined, as it was in our study.

The recognition deficit in the present study cannot be attributed to differences in difficulty between verbal and nonverbal items because the normal control subjects scored equally well on both content recognition tests (total verbal score = 82%; total nonverbal score = 80%). Furthermore, problems in visual perception (Boller *et al.*, 1984) alone could not entirely account for the PD deficit because, at the long intervals, content recognition of the PD group rose to the normal range (for further argument, *see* Sullivan and Sagar, 1988 and Sullivan *et al.*, 1989). Instead, the present results and those from the verbal study (Sagar *et al.*, 1985, 1988*b*) etsablish impairment in verbal and nonverbal short-term recognition, with relative sparing of long-term recognition, as specific deficits in clinically treated PD patients, regardless of their overall mental status. We propose that this short-term memory deficit in PD underlies the clinical phenomenon of bradyphrenia. A bradyphrenic response is slow but, if the responder is given sufficient time, is accurate. As reported for verbal material (Sagar *et al.*, 1988*b*), recognition of nonverbal material was poor when tested soon after stimulus presentation but improved to normal at longer intervals. Whatever the cognitive mechanism, the results of the verbal and nonverbal studies suggest that our paradigm provides experimental support for the clinical observation of slowed response that has been termed bradyphrenia.

It may be argued that recognition of the designs presented at the shortest stimulus-test interval was not perfect because those designs were intrinsically more difficult to remember than were the designs tested at the longer intervals. Furthermore, if true, this difficulty may be exaggerated in patients with memory deficits. Evidence exists, however, to refute this possibility. Results obtained with this same test in the severely amnesic patient H.M. indicate that while his content recognition at the long intervals was clearly impaired, his performance at the interval of 1 was on par with normal control subjects (Sagar *et al.*, 1984).

Processing differences of verbal and nonverbal material

Within the normal control group, as well as the patient groups, verbal and nonverbal recognition forgetting curves for content information differed qualitatively, even though the total content scores were virtually identical for both classes of information. Recognition of verbal material, unlike that of nonverbal material, followed a classical forgetting function: the accuracy of verbal content judgements decreased with increasing stimulus-test interval from 100 to 64% whereas the accuracy for nonverbal judgements remained at about 80% regardless of number of intervening items. The flat forgetting curve of the healthy control group for nonverbal content permitted group comparisons to be made at the short as well as the long retention intervals that were not possible in the verbal test because of the ceiling effect at the delay of 1 on the verbal test.

Differences in forgetting levels for different classes of information are well documented in normal subjects and are thought to reflect fundamental distinctions between verbal and nonverbal information processing (Sullivan and Turvey, 1972, 1974; Erdelyi and Becker, 1974). The perfect recall and recognition of verbal material after short uninterrupted intervals has been attributed to a proficiency of verbal encoding, rehearsal, or retrieval (Craik and Watkins, 1973; Woodward *et al.*, 1973); the longevity of visual, nonverbal traces, by contrast, has been attributed to that system's resistance to interference and to opportunities to use mnemonic strategies based upon imagery, which is naturally supplied by visual displays (Paivio, 1971; Kroll and Kellicutt, 1972; Anderson and Bower, 1973; Potter, 1976; Pylyshyn, 1979). The results of this study thus provide support for functional distinctions in the processing of different classes of material analogous to the anatomical distinction reported in patients with unilateral focal cortical excision (e.g., Milner, 1971, 1982).

For recency discrimination, but not content recognition, the verbal and nonverbal retention functions declined as the intervals lengthened. The primary difference between the two classes of material in the case of recency discrimination was quantitative, that is, verbal recency judgements were accurate more often than were nonverbal judgements.

Conclusion

The finding of deficits in nonverbal recognition and recency discrimination adds to the growing list of specific cognitive deficits in PD and further questions the adequacy of nonspecific assessment scales in detecting subtle cognitive impairments that contribute to a diagnosis of dementia (*see* Sagar and Sullivan, 1988). In addition, the observations that PD and AD differ in the relationship between recency discrimination and dementia severity and between short-term and long-term memory support the notion that the two diseases differ in cognitive profile (*see* Sullivan *et al.*, 1985, 1989; Sagar, 1987; Sagar *et al.*, 1988*b*; Sullivan and Sagar, 1988).

Characteristic patterns of cognitive impairment in different diseases presumably reflect the specific pathology of each condition. AD ultimately results in the demise of virtually all cognitive functions, including various components of memory (e.g., Corkin, 1982; Corkin *et al.*, 1986; Sullivan *et al.*, 1986; Sagar *et al.*, 1988*a*), praxis (e.g., Rosen and Mohs, 1982; Huff and Growdon, 1986), visuospatial orientation and discrimination (e.g., Nissen *et al.*, 1985; Huff *et al.*, 1986), and so-called executive function (Pribram, 1971; Luria, 1980; Baddeley, 1986; Stuss and Benson, 1987) thought to be reliant on the integrity of the frontal lobes. Postmortem pathological studies of AD have shown significant disruption of anatomical and neurochemical, cortical and subcortical substrates serving such functions and include the limbic system, especially the hippocampus and amygdala, the basal forebrain nuclei, and the parietal and frontal cortex (e.g., Blessed *et al.*, 1968; Perry *et al.*, 1978; Brun and Englund, 1981; Chase, 1984; Price *et al.*, 1985). In PD, the cognitive and pathological changes are more restricted than in AD. Specific cognitive functions that have been reported as deficient in PD include verbal and nonverbal recency discrimination (Sagar *et al.*, 1985, 1988*b*; Sullivan *et al.*, 1985; this report), dating of remote memories (Sagar *et al.*, 1985, 1988*a*), verbal and nonverbal short-term memory (Sagar *et al.*, 1985, 1988*b*; Taylor *et al.*, 1986*a*; Sullivan and Sagar, 1988), planning (Lees and Smith, 1983; Cools *et al.*, 1984), sequencing (Stern *et al.*, 1983; Sullivan *et al.*, 1985, 1989), set shifting and formation (Bowen, 1976; Sullivan *et al.*, 1985, 1989), and visuospatial function (Proctor *et al.*, 1964; Boller *et al.*, 1984). The pathology of PD involves particular subcortical structures, including the substantia nigra and ventral tegmentum, but also ascending dopaminergic projections from these subcortical sites to cortical targets. Noradrenergic and cholinergic systems with major sites of origin in the locus coeruleus, nucleus basalis of Meynert, and striatum (Graybiel *et al.*, 1986), are also disrupted in PD (Forno and Alvord, 1974; Hornykiewicz, 1982; Ruberg *et al.*, 1982; Whitehouse *et al.*, 1983; Cash *et al.*, 1984; Nakano and Hirano, 1984). Specific cortical targets of these basal ganglia projections are the dorsolateral prefrontal cortex, lateral orbitofrontal cortex, frontal eye fields, supplementary motor cortex and anterior cingulate area (Nauta and Domesick, 1978; Graybiel, 1984; Alexander *et al.*, 1986). In positron emission tomography studies, the extent of cortical glucose utilization reduction has been related to severity of parkinsonian dementia and bradykinesia (Kuhl *et al.*, 1984).

Taken together, this evidence suggests that the specific cognitive dysfunction could result from disconnection of critical cortical sites, notably in the frontal lobes, due to dysfunction in a number of subcortical projection systems (e.g., Sagar, 1985; Pillon *et al.*, 1986; Taylor *et al.*, 1986*b*; Sagar and Sullivan, 1988). Although frontal lobe deficits are recognized in untreated PD (Lees and Smith, 1983), the effects of treatment and the influence of age and disease duration have been little examined. Differential effects on different frontal lobe functions may result from levodopa therapy (Gotham *et al.*, 1986) but the factors influencing frontal lobe function in PD have only just begun to be explored. Studies of the effects of specific pharmacological manipulation of subcortical projection systems may provide valuable evidence of the neurochemical origin of cognitive deficits in PD and provide a rationale for the pharmacological treatment of cognitive disorders.

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CONDUCTION VELOCITIES OF MUSCLE AND CUTANEOUS AFFERENTS IN THE UPPER AND LOWER LIMBS OF HUMAN SUBJECTS

by GARY MACEFIELD, SIMON C. GANDEVIA *and* DAVID BURKE

(*From the Unit of Clinical Neurophysiology, Department of Neurology, The Prince Henry Hospital and School of Medicine, University of New South Wales, Sydney, Australia*)

SUMMARY

In the cat and monkey the fastest axons in the peripheral nerve are group I afferents from muscle, but there are no definitive data on conduction velocity for these afferents in human subjects. Knowledge of the relative conduction velocities of muscle and cutaneous afferents is important for the interpretation of reflex studies, evoked potentials and other aspects of motor control. To rectify this deficiency, the conduction velocities of the fastest muscle and cutaneous afferents were determined for the median, ulnar and tibial nerves of normal subjects. Low-threshold muscle afferents innervating abductor pollicis brevis, abductor digiti minimi and abductor hallucis were stimulated selectively through a microelectrode inserted percutaneously at the motor point. Low-threshold cutaneous afferents were stimulated with ring electrodes around the proximal phalanx of digits II or V for the upper limb and digit II for the lower limb. Compound action potentials were recorded with bipolar near-nerve electrodes at two sites in the proximal limb segment and conduction velocities of the fastest afferents in the neural volley calculated. The mean conduction velocities of the muscle and cutaneous afferents were, respectively, $74.7 \pm 6.5\ \mathrm{m \cdot s^{-1}}$ and $80.3 \pm 6.7\ \mathrm{m \cdot s^{-1}}$ for the median nerve, $67.5 \pm 10.2\ \mathrm{m \cdot s^{-1}}$ and $67.5 \pm 10.5\ \mathrm{m \cdot s^{-1}}$ for the ulnar nerve, and $54.7 \pm 3.4\ \mathrm{m \cdot s^{-1}}$ and $52.8 \pm 3.2\ \mathrm{m \cdot s^{-1}}$ for the tibial nerve. For upper and lower limb nerves the conduction velocities of low-threshold muscle and cutaneous afferents were not significantly different when measured over the same proximal segment.

INTRODUCTION

Little is known about the conduction velocities of human group I muscle afferents and most texts accept data from the cat as being appropriate for man. In the hindlimb of the cat the modal conduction velocity of individual Ia afferents from soleus is 100–110 $\mathrm{m \cdot s^{-1}}$ (range 60–125 $\mathrm{m \cdot s^{-1}}$; Hunt and Kuffler, 1951), whereas that for a population of low-threshold cutaneous afferents in the saphenous nerve is 54–60 $\mathrm{m \cdot s^{-1}}$ (range 33–95 $\mathrm{m \cdot s^{-1}}$; Brown and Iggo, 1967). Conduction velocities in the primate are slower but, as in the cat, muscle afferents conduct faster than cutaneous afferents: in the baboon the majority of Ia afferents from soleus conduct at 80–85 $\mathrm{m \cdot s^{-1}}$ (Cheney and Preston, 1976), and in the monkey the mean conduction velocity of low-threshold mechanoreceptors from the skin of the foot is $38 \pm 6\ \mathrm{m \cdot s^{-1}}$ (Lindblom, 1965).

The conduction velocities of low-threshold muscle afferents in human subjects have been estimated indirectly from differences in H reflex latency either of the thenar muscles

Correspondence to: Dr G. Macefield, Unit of Clinical Neurophysiology, The Prince Henry Hospital, PO Box 233, Matraville, Sydney, Australia 2036.

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when stimulating the median nerve at two sites in the forearm (Eisen *et al.*, 1984; Deuschl *et al.*, 1985) or of the tibial nerve when stimulating at two sites in the thigh (Abbruzzese *et al.*, 1985). Estimates have also been made by Abbruzzese *et al.* (1985) using afferent volleys evoked by tendon percussion. However, tendon percussion does not activate intramuscular afferents selectively; the resultant volleys are contaminated by cutaneous afferent activity (Burke *et al.*, 1983). Electrical stimulation of the tibial and sural nerves at the ankle allows conduction velocities of muscle and cutaneous afferents from the foot to be compared, albeit indirectly (Burke *et al.*, 1981; Gandevia *et al.*, 1982; Bartel *et al.*, 1985; Vogel *et al.*, 1986). The tibial nerve at the ankle is a mixed nerve, containing afferents of muscle, cutaneous and articular origin; the sural nerve is primarily cutaneous from the lateral aspect of the foot but also conveys joint afferents from the ankle (Gardner *et al.*, 1975). The most rapidly conducting afferents of the tibial nerve appear to be $5-10\ \mathrm{m \cdot s^{-1}}$ faster than those of the sural nerve across the distal limb segment, and this has been attributed to the presence in the tibial nerve of group I muscle afferents (Burke *et al.*, 1981; Gandevia *et al.*, 1982). This comparison, however, is based on the assumptions that nerve length and temperature were the same.

To activate human muscle afferents directly, without the coactivation of cutaneous and joint afferents when stimulating a mixed nerve, low-threshold sensory and motor axons were activated by constant-current pulses delivered through an insulated microelectrode inserted percutaneously at the motor point (Gandevia and Burke, 1986, 1988). The technique has been employed to demonstrate the cortical projections of low-threshold muscle afferents from several proximal and distal muscles of the upper limb (Gandevia and Burke, 1988) and from abductor hallucis (Macefield *et al.*, 1988*a*). The present study was designed to measure the conduction velocities of the fastest afferents of muscle origin and those of cutaneous-articular origin in the proximal segment of the upper and lower limbs of human subjects. In each limb conduction velocities were compared over the same conduction distance using identical recording conditions. The results indicate that, in contrast to data from the cat and monkey, low-threshold muscle afferents do not conduct more rapidly than low-threshold cutaneous afferents in normal human subjects. A preliminary report of some of the results has been published (Macefield *et al.*, 1988*b*).

METHODS

Nerve conduction data from the upper limb were obtained in 8 healthy subjects, each of whom provided informed consent. The experiments were conducted with the approval of the institutional ethics committees. Six of the subjects were 21−33 yrs of age, 1 was 43 and another 59. Nerve conduction data from the lower limb were obtained in 6 of the 8 subjects (age 21−43 yrs). Experimental sessions were generally of 2−3 h duration.

Stimulation procedures

The median or ulnar nerve at the wrist was stimulated by constant-current pulses (0.3 ms, 3 Hz) delivered through bipolar surface electrodes (cathode proximal) at a level sufficient to produce pronounced activation of the appropriate intrinsic muscles *and* radiating cutaneous sensations, neither of which the subjects considered noxious. The digital nerves of digit II or V were stimulated at 2–3 times perceptual threshold via ring electrodes around the proximal phalanx (cathode proximal) or, in 3 subjects, around the distal phalanx. In addition, in 3 subjects the proximal phalanx of digits II and/or III were stimulated at 1.5–2.0 times perceptual threshold. Low-threshold muscle afferents of abductor pollicis brevis (median innervation) or abductor digiti minimi (ulnar innervation) were stimulated with constant-current pulses (0.3 ms, 3 Hz, 1–3 mA) delivered through a tungsten microelectrode, insulated except for approximately 200 μm at its tip, inserted percutaneously at the motor point (Gandevia and Burke, 1986, 1988; Macefield *et al.*, 1988*a*,*b*). The motor point was initially localized using stimuli delivered through a surface probe. The anode was a surface electrode on the dorsum of the hand. The intramuscular stimuli caused a clear twitch confined to the appropriate muscle but no cutaneous sensations (local or radiating) and no deep sensations referred to distal joints (*see* Gandevia and Burke, 1988). They were not considered noxious.

The tibial nerve at the medial malleolus was stimulated through surface electrodes (cathode proximal) with constant-current pulses (0.3 ms, 3 Hz) at a level sufficient to produce a clear twitch contraction of the intrinsic muscles of the foot *and* radiating cutaneous sensations that were not noxious. The sural nerve at the lateral malleolus and the digital nerves of digit II (proximal phalanx) were stimulated at 2–3 times sensory threshold. Low-threshold muscle afferents of abductor hallucis were stimulated through an insulated tungsten microelectrode inserted percutaneously at the motor point with the anode on the dorsum of the foot.

Recording procedures

For the studies of conduction in the upper limb the subject lay supine with the shoulder abducted 30–40° and the arm extended. Constant-current stimuli delivered through a surface probe (2 mm diameter) were used to locate the median nerve in the cubital fossa and axilla and the ulnar nerve behind the medial malleolus and in the axilla. Platinum-alloy needle electrodes (shaft length 10 mm) were inserted subdermally in a longitudinal bipolar configuration, with an interelectrode separation of 40 mm. This configuration is considered to be optimal in minimizing the contribution of the reference electrode to the recorded compound action potential (Eduardo and Burke, 1988). Referential recordings were also made using a common reference electrode inserted lateral to the course of the nerve and intermediate to the proximal and distal electrode sites. For the studies of conduction on the lower limb the subject lay prone and the optimal recording sites of the tibial nerve at the popliteal fossa and upper thigh were located using a surface probe. Tungsten microelectrodes (shaft length 55 mm), insulated to within 10 mm of the tip, were inserted percutaneously in a bipolar configuration (interelectrode separation 40 mm) and their final location adjusted while delivering constant current stimuli through the electrode. A ground electrode was applied distal to the recording sites. Skin temperature over the conduction path was maintained at ±0.5° C within the range 32–35° C. The conduction distance along the proximal limb segment was determined with a tape measure applied to the skin between the active recording electrodes and its value verified at the conclusion of the experiment. The ranges of conduction distances were 110–180 mm and 180–225 mm for the upper and lower limbs, respectively.

Compound nerve action potentials were amplified (5×10^4), filtered (bandpass 10 Hz–1.5 kHz) and digitized at 10 kHz (Medelec Sensor ER-94A). For studies of the upper limb, potentials were analysed over 20 ms following delivery of the stimulus; for the lower limb studies the potentials were analysed over 30 ms. Repeated averages of 256 sweeps were directed alternately to two stores, generating duplicate averages each totalling 256–4096 sweeps. Mutiple sets of averages were obtained in some subjects. Data were stored on disc and analysed off-line.

Analysis

For each subject grand averages of the bipolar and referential data were derived from the duplicate or multiple records. Latencies of the potentials were measured by cursor from the onset of the stimulus to the onset of the major negative phase (initial positive peak). Correct placement of the cursor at the peak was facilitated by monitoring the difference in amplitude between the marking cursor and a reference cursor.

No attempt was made to improve the temporal resolution of the system by interpolating between two steps of the cursor; the error in measurement of latency should be equally distributed in the directions of over-estimation and under-estimation. For recordings in the upper limb amplitudes were determined from the referential records as the peak of the initial positive phase to the peak of the major negative phase. However, in the lower limbs, the afferent volleys were more dispersed and the amplitude of the potential reflected the intensity of the volley less accurately.

It has been repeatedly demonstrated that, in normal human subjects, the fastest axons contributing to the compound nerve action potential produced by stimulating a mixed nerve are afferent, not efferent, having conduction velocities some 5 – 10 $m \cdot s^{-1}$ faster than the fastest motor axons in that nerve (Dawson, 1956; Gilliatt *et al.*, 1961; Buchthal and Rosenfalck, 1966; Melvin *et al.*, 1966; Behse and Buchthal, 1971; Dorfman, 1984; Abbruzzese *et al.*, 1985). This has been confirmed for 4 of the 8 subjects in the present study (*see* Burke *et al.*, 1981, 1983; Gandevia *et al.*, 1982). It is therefore assumed that the fastest fibres in the mixed nerve action potential are afferent not efferent and that with motor point stimulation the fastest axons are afferent (presumably group I) not efferent (*see* Discussion).

Analysis of variance was employed to evaluate the statistical significance of the data. Differences were considered significant at the $P<0.05$ level.

RESULTS

Conduction velocities of afferents in the upper limb

Compound action potentials generated by electrical stimulation of the median or ulnar nerves at the wrist, the proximal phalanx of digits II or V, and the motor point of abductor pollicis brevis or abductor digiti minimi were recorded at the elbow and axilla using both bipolar and referential electrode configurations. Representative examples of afferent conduction in the whole nerve and its constituent muscle and cutaneous-articular fascicles are illustrated for the median and ulnar nerves in figs 1 and 2, respectively. As indicated in Table 1, the conduction velocities of the fastest muscle afferents of abductor pollicis brevis and abductor digiti minimi were not significantly different from those of the fastest afferents (cutaneous and articular) innervating digits II and V, respectively. Also, the conduction velocities were not significantly different from the most rapidly conducting components of the volley produced by stimulation of the parent nerve at the wrist (Table 1). In 3 subjects the digital nerves were stimulated at the distal phalanx to avoid the activation of interphalangeal joint afferents that occurs when stimuli are delivered at the proximal phalanx (*see* Discussion). There was no difference in conduction velocity of the digital potentials evoked from the two sites, suggesting that the conduction velocities of the fastest articular afferents were not greater than those of the fastest cutaneous afferents.

Amplitudes of the neural volleys at the proximal and distal sites, measured from the referential recordings, are presented in Table 2 and expressed both in absolute and relative terms. Data for the median and ulnar nerves were pooled because there were no significant differences in the sizes of their compound action potentials. The diminution in amplitude at the proximal recording site relative to the distal site (Kimura *et al.*, 1986; Olney *et al.*, 1987) was independent of size of the afferent volley. However, temporal dispersion of the afferent volley, measured as the increase in rise-time of the potential across the 110 – 180 mm separating the distal and proximal recording sites (mean conduction

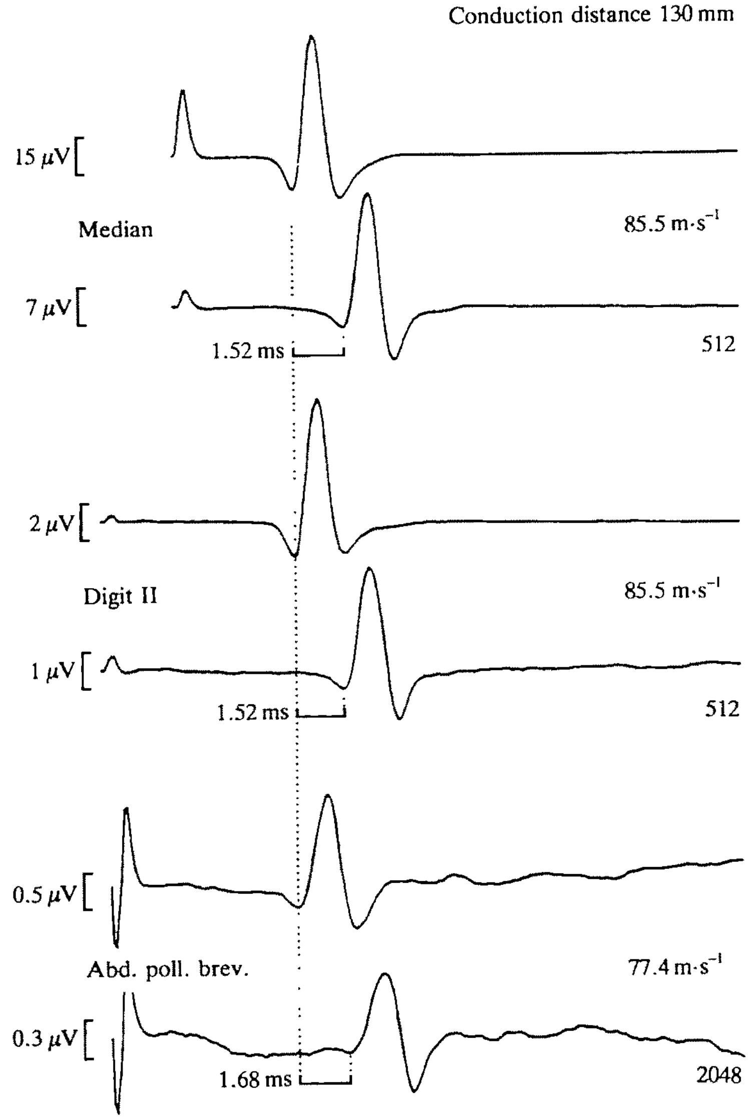

FIG. 1. Compound action potentials generated by stimulation of the median nerve at the wrist and its cutaneous-articular and muscle afferent components in one subject (male, 21 yrs). Upper and lower records in each panel are the potentials recorded with bipolar electrodes at the cubital fossa and the axilla, respectively. Panels are aligned with respect to the arrival of the afferent volley at the cubital fossa. Numbers of sweeps comprising each average (i.e., the grand average of duplicate subaverages) are indicated at the lower right of each panel. Note that the calculated conduction velocity of the fastest muscle afferents is not greater than that of the fastest cutaneous-articular afferents.

distance 138 mm), was dependent on the amplitude of the afferent volley. The smaller volleys generated by stimulation of only cutaneous or only muscle afferents exhibited significantly less temporal dispersion than the potentials produced by stimulation of the parent nerve (Table 2).

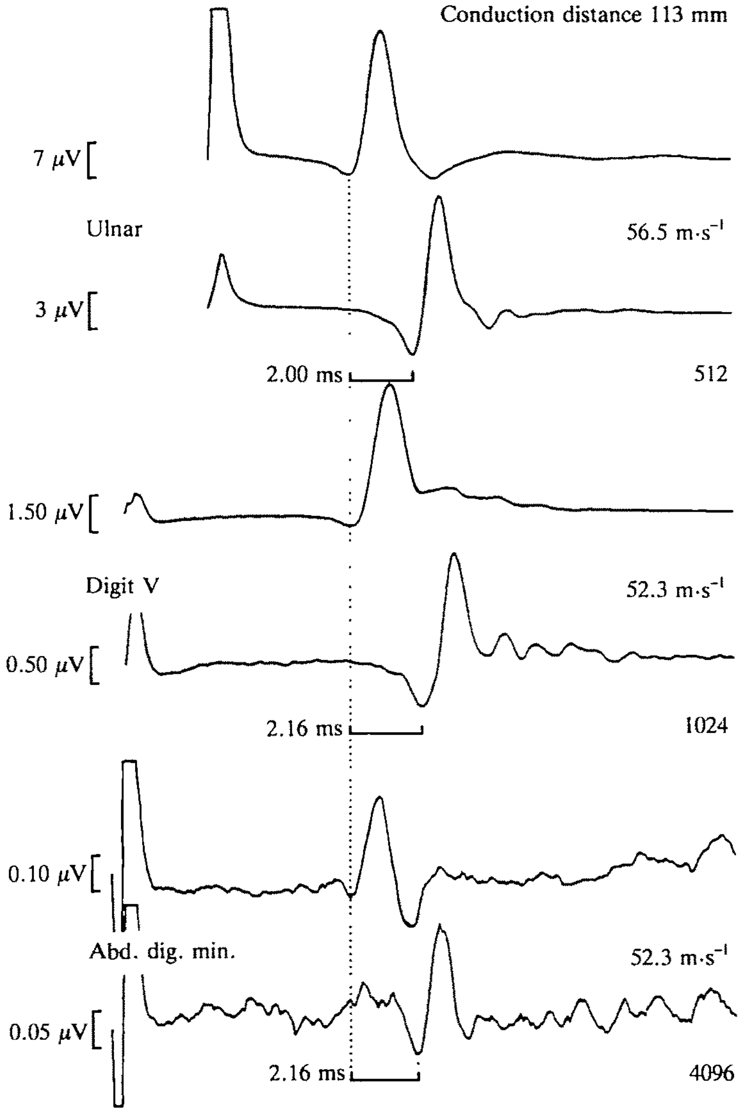

FIG. 2. Compound action potentials generated by stimulation of the ulnar nerve at the wrist and its cutaneous-articular (proximal phalanx of digit V) and muscle (abductor digiti minimi) afferent components in 1 subject (male, age 26 yrs). Upper and lower records in each panel are the potentials recorded with bipolar electrodes behind the medial malleolus and at the axilla, respectively. The calculated conduction velocities of the fastest muscle and cutaneous-articular afferents are identical.

Both amplitude and temporal dispersion of the potential influence the shape of the initial positive peak and therefore the definition of onset latency. The greater definition afforded by a potential with a larger amplitude may be confounded by the problems of temporal dispersion. The effect of amplitude on the measured difference in latency between the distal and proximal recording sites was examined in 3 subjects by delivering

TABLE 1. MEAN ± SD CONDUCTION VELOCITY DATA ($m \cdot s^{-1}$) FOR THE PROXIMAL SEGMENT OF THE UPPER LIMB, DETERMINED FROM BIPOLAR AND REFERENTIAL RECORDS*

	Bipolar	*Referential*		*Bipolar*	*Referential*
Median	81.1 ± 6.7 (69.0–89.3) n = 7	81.4 ± 10.8 (63.9–94.1) n = 6	Ulnar	72.7 ± 11.1 (56.5–83.3) n = 5	74.2 ± 13.6 (54.3–83.3) n = 6
Digit II	80.3 ± 7.1 (65.2–85.9) n = 7	75.8 ± 10.8 (65.2–88.9) n = 6	Digit V	67.5 ± 10.5 (52.3–78.1) n = 5	68.5 ± 12.3 (48.7–81.7) n = 6
APB	74.7 ± 6.5 (63.9–89.3) n = 7	74.8 ± 8.0 (63.9–84.2) n = 7	ADM	67.5 ± 10.2 (59.0–78.9) n = 5	63.9 ± 10.7 (50.4–78.7) n = 6

* Ranges in brackets; n = number of subjects, APB = abductor pollicis brevis, ADM = abductor digiti minimi.

TABLE 2. REDUCTION IN AMPLITUDE AND TEMPORAL DISPERSION OF THE NEURAL VOLLEY IN THE PROXIMAL SEGMENT OF THE UPPER LIMB, DETERMINED FROM REFERENTIAL RECORDS*

	Amplitude at elbow (μV)	*Amplitude at axilla (μV)*	*Relative amplitude at axilla*	*Temporal dispersion (%/100 mm)*
Median and ulnar n = 12	53.8 ± 19.6 (19.1–87.0) [1.00]	23.7 ± 11.4 (12.5–51.8) [1.00]	0.44	27.9 ± 16.9 (0–54.7)
Digits II and V n = 13	7.5 ± 2.9 (2.5–14.8) [0.14]	3.4 ± 1.8 (1.5–6.4) [0.14]	0.45	19.9 ± 14.9 (0–56.8)
APB and ADM n = 12	1.4 ± 0.9 (0.2–3.2) [0.03]	0.6 ± 0.4 (0.1–1.3) [0.03]	0.43	18.1 ± 12.9 (0–37.7)

* Ranges of amplitudes of the potentials recorded at the elbow and axilla are given in round brackets, relative amplitudes in square brackets; n = number of subjects. Temporal dispersion was calculated as the increase in rise-time of the potential recorded at the axilla, relative to the elbow, expressed as percentage increase per 100 mm.

low-intensity stimuli (1.5–2.0 × sensory threshold) to the proximal phalanx of digits II or III, either independently or simultaneously. Neural volleys were recorded with bipolar electrodes over the median nerve at the wrist and cubital fossa (conduction distance 240–255 mm). In each subject, stimulus sites were adjusted so that the latencies of the potentials recorded at the wrist were the same for the two digits. When the size of the recorded potential was increased by delivering simultaneous stimuli to the two digits the onset latency of the potential decreased more at the proximal site than the distal (by up to 0.3 ms). These small differences translated into increases in conduction velocity of 2–4 $m \cdot s^{-1}$. Comparable changes in conduction velocity with increasing stimulus intensity are seen in fig. 1 of Rosenfalck and Buchthal (1973). It is concluded that the amplitude of the recorded potential can influence the resolution of latency differences and hence the calculation of velocity (*see also* below).

Conduction velocities of afferents in the lower limb

Low-threshold muscle afferents of abductor hallucis did not conduct significantly faster than the low-threshold cutaneous afferents from digit II, as assessed from bipolar recordings (Table 3). The conduction velocities were slower than those of the parent nerve (tibial nerve at ankle) and those of the sural nerve, but the differences were not statistically significant. As noted above, the small differences in calculated conduction velocity may be a reflection of the larger size of the tibial and sural nerve volleys (*see also* Rosenfalck and Buchthal, 1973); when the stimulating current to the sural nerve was reduced in 2 subjects, such that the afferent volley approached the amplitude of the potential from digit II, the calculated conduction velocity was 4–8 m·s^{-1} less (fig. 4).

As illustrated in fig. 3, all potentials were fractionated (Behse and Buchthal, 1971)

TABLE 3. MEANS ± SD FOR CONDUCTION VELOCITY DATA (m·s^{-1}) FOR THE PROXIMAL SEGMENT OF THE LOWER LIMB, DETERMINED FROM BIPOLAR RECORDS*

Tibial nerve	*Sural nerve*	*Abductor hallucis*	*Digit II*
57.9 ± 1.9	56.3 ± 3.7	54.7 ± 3.4	52.8 ± 3.2
(56.0–60.0)	(52.4–62.5)	(50.6–58.6)	(47.5–55.6)
n = 6	n = 6	n = 6	n = 6

* Ranges in brackets; n = number of subjects.

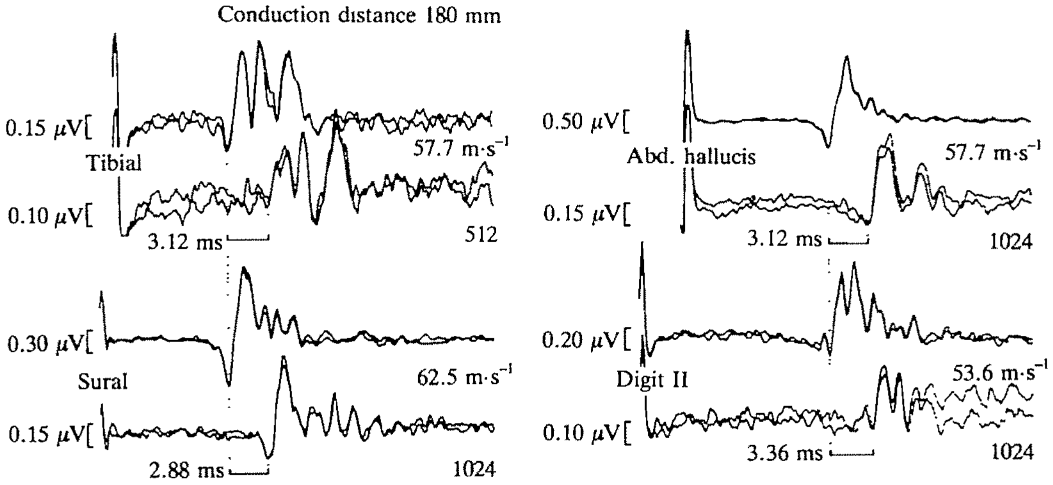

FIG. 3. Compound action potentials generated by stimulation of the tibial and sural nerves at the medial and lateral malleolus, respectively, and the muscle (abductor hallucis) and cutaneous-articular (proximal phalanx of digit II) afferent components of the posterior tibial nerve, in one subject (female, age 31 yrs). Upper and lower records in each panel are the potentials recorded with bipolar electrodes at the popliteal fossa and at the upper thigh, respectively. Duplicate subaverages are provided to illustrate the reproducibility of the recordings; latencies were measured from the grand average, the number of sweeps comprising which is included at the lower right of each panel. Note that in this example the conduction velocity of the afferent volley from the digit is calculated for the fastest axons in the major component of the fractionated potential; the conduction velocity of the fastest afferents of the volley, i.e., the small potential preceding the initial major negativity, was calculated to be 71.4 m·s^{-1}.

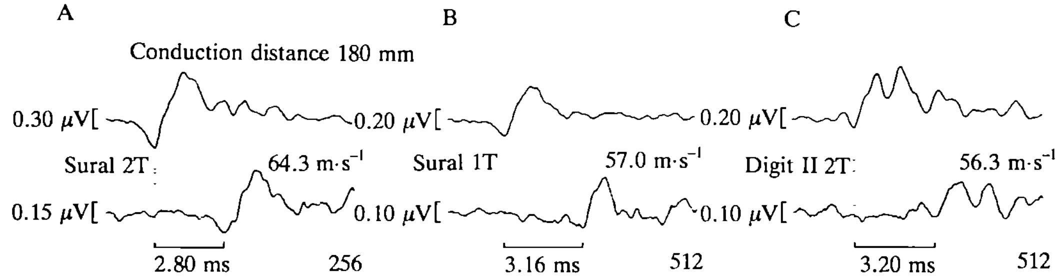

FIG. 4. The effect of stimulus intensity on the apparent conduction velocity of afferents from the sural nerve in the same subject as in fig. 3. *Upper and lower records* are the potentials (grand averages) recorded with bipolar electrodes from the popliteal fossa and upper thigh, respectively; the time base is expanded relative to that in fig. 3. The records in A and B commence 8.0 ms following the delivery of the stimulus, and those in C are preceded by 12.0 ms. When the sural nerve at the medial malleolus was stimulated at sensory threshold (B), such that the afferent volley was comparable in amplitude to the volley from stimulation of the digit (C), the conduction velocity of the neural volley was less than that resulting from stimulation of the sural nerve at twice sensory threshold (A).

due to the temporal dispersion between the foot and popliteal fossa and along the 180–225 mm femoral conduction segment (mean distance 203 mm). Because of the separation of the afferent volley into multiple components, the decline in amplitude between the distal and proximal recording sites was not quantified, although such attenuation did occur (figs 3, 4). The fractionation also resulted in poor definition of the onset latency in some instances. The latency was therefore defined in such cases as the major positive peak preceding the dominant negative peak, because this would reflect the arrival of the volley from the majority of the fastest afferents at the active recording electrode. For example, in fig. 3 the initial negative component of the afferent volley from the digit conducted at 71.4 $m \cdot s^{-1}$, whereas the afferents responsible for the major component conducted at 53.6 $m \cdot s^{-1}$.

The values quoted in Table 3 thus represent the fastest *population* of afferents in each volley, excluding isolated faster-conducting small components. This was considered acceptable because conventional measurements made on compound action potentials do not reflect the activity of the fastest axons in the neural volley but instead the velocity of the dominant population (*see* Buchthal and Rosenfalck, 1966; Dorfman, 1984).

DISCUSSION

Conduction velocities of muscle and cutaneous afferents

This study has determined the peripheral conduction velocities of low-threshold muscle afferents in the median, ulnar and tibial nerves of normal human subjects and demonstrated that the fastest muscle afferents do not conduct along the proximal limb segment more rapidly than the fastest cutaneous/articular afferents of the digital nerves. On the basis of electrical excitability of human nerves Dawson (1956) had concluded that the conduction velocities of low-threshold afferents from the thenar muscles are not greater than those of the digital nerves. By comparing the relationship of H and long-latency reflexes evoked by stimulation of the median nerve with the long-latency reflexes evoked by stimulation of the cutaneous superficial radial nerve, Deuschl *et al.* (1985) concluded that the conduction velocities of the cutaneous afferents mediating the long-latency reflex are in the range of the low-threshold muscle afferents. The present study provides direct support for these conclusions.

According to Stilwell (1957) the distal interphalangeal joint receives an articular branch of the digital nerve that enters the joint proximally. When the digital nerves are stimulated at the distal phalanx, the resultant afferent potential will therefore contain cutaneous activity from the finger tip without contamination by articular activity. The conduction velocities of the afferent volleys generated by stimulation of the distal phalanx and the proximal phalanx were similar, such that the digital nerve conduction data probably reflect the conduction of low-threshold cutaneous afferents. That the conduction velocities of low-threshold muscle and cutaneous afferents were not significantly different suggests that their populations share a similar range of axonal diameters. Certainly, the unitary action potentials recorded from identified sensory axons originating in muscle spindle, cutaneous and articular receptors of the hand are comparable in amplitude, as reported in a recent microneurographic study in normal subjects (Burke *et al.*, 1988).

Stimulation of low-threshold muscle afferents

Intramuscular electrical stimulation allows selective activation of muscle afferents without some of the limitations inherent in microneurographic studies: intraneural stimulation of muscle afferents within motor fascicles is possible only with nerves that are readily accessible, such as the median, ulnar, radial and tibial nerves, and is not suitable for the study of proximal muscles (Gandevia and Burke, 1986, 1988). The afferents activated by microstimulation at the motor point were of low threshold, were activated at levels close to motor threshold, and conducted rapidly. It is well known that the fastest motor axons conduct slower than the fastest sensory axons in a mixed nerve (Dawson, 1956; Gilliatt *et al.*, 1961; Buchthal and Rosenfalck, 1966; Melvin *et al.*, 1966; Behse and Buchthal, 1971; Burke *et al.*, 1981; Gandevia *et al.*, 1982, 1984; Dorfman, 1984; Abbruzzese *et al.*, 1985). Hence it can be assumed that the initial component of the neural volley initiated by stimulation at the motor point consisted of orthodromically activated sensory axons rather than antidromically activated motor axons and, in accordance with this view, well-defined sensory evoked potentials can be recorded over the scalp at appropriately short latencies (Gandevia and Burke, 1988; Macefield *et al.*, 1988*a*). Along the distal limb segment the mean conduction velocities of the fastest motor axons to abductor pollicis brevis, abductor digiti minimi and abductor hallucis, as determined from compound muscle action potentials, are $57.2 \pm 4.2\ \text{m}\cdot\text{s}^{-1}$, $56.2 \pm 4.6\ \text{m}\cdot\text{s}^{-1}$ and $43.2 \pm 4.9\ \text{m}\cdot\text{s}^{-1}$, respectively (Thomas *et al.*, 1959); the corresponding conduction velocities of the compound sensory volleys along the proximal segment are $74.7 \pm 6.5\ \text{m}\cdot\text{s}^{-1}$, $67.5 \pm 10.2\ \text{m}\cdot\text{s}^{-1}$ and $54.7 \pm 3.4\ \text{m}\cdot\text{s}^{-1}$ (present data).

The low-threshold afferents activated by intramuscular stimulation were not cutaneous in origin: the exposed tip of the insulated microelectrode was located at least 5 mm within the muscle belly such that it would be highly unlikely that the stimuli would cause local activation of cutaneous afferents. The subjects did not report local cutaneous sensations associated with the stimuli, nor did they report radiating paraesthesiae. Cutaneous receptors would have been stimulated by the muscle twitch but not until appreciable skin distortion had occurred, too late to contribute to the neural volley. As discussed by Gandevia and Burke (1988), the afferents activated by intramuscular stimulation most likely belong to the group I population, originating in the primary ending of the muscle spindle (group Ia) and the Golgi tendon organ (group Ib). Devanandan *et al.* (1983) have demonstrated a rich supply of muscle spindles but a relative paucity of Golgi tendon organs in the intrinsic muscles of the monkey hand. In the course of microneurographic studies of afferents from the hand in normal human subjects we have encountered many afferents possessing the properties of muscle spindles but few possessing those of Golgi tendon organs (*see* Burke *et al.*, 1988), suggesting that in the human hand the relative proportions of the two receptor types may be similar to those in the monkey. Intramuscular stimulation of intrinsic muscles of the hand may therefore be a relatively selective stimulus for muscle spindle afferents.

Implications

In previous studies from this laboratory, it has been asserted that, in the human lower limb, muscle afferents conduct some 5–10 $m \cdot s^{-1}$ faster than cutaneous afferents (Burke *et al.*, 1981, 1982, 1983; Gandevia *et al.*, 1982). This view was based on comparisons of the conduction velocities of the tibial mixed nerve potential and the sensory potential of the sural nerve when stimulated at the ankle and recorded at the popliteal fossa. These studies used different stimulus intensities for the two nerves and assumed that the conduction paths were equally direct for the two neural volleys. In the present study, conduction time was measured across the identical segment of the sciatic nerve for each afferent volley and the effects of stimulus intensity were eliminated by determining the conduction time between two recording sites. Nevertheless, there was still a tendency for the larger, better defined volleys to have a slightly shorter conduction time than the smaller volleys.

Some of the conclusions from this laboratory should be reappraised in the light of the present findings. It has been a consistent theme of our studies that the cerebral potential evoked by stimulation of mixed nerves in the lower limb (such as the tibial nerve) is determined largely if not exclusively by muscle afferents. The shorter latency of P40 of the cerebral potential to tibial nerve stimulation when compared with that produced by sural nerve stimulation (some 5 ms) was attributed to a combination of faster peripheral conduction and faster central conduction of muscle afferent volleys (Burke *et al.*, 1981, 1982; Burke and Gandevia, 1986). Vogel *et al.* (1986) provided evidence that most of the discrepancy in latency of P40 was due to faster central conduction, a view with which we fully concur. However, this is consistent with our argument that the cerebral potentials to stimulation of the tibial and sural nerves are determined by different afferent populations, presumably muscle afferent and cutaneous afferent, respectively (*cf.* Kakigi and Jones, 1986). This view is further supported by topographic differences in the cerebral projection of these nerves as recorded using magnetoencephalography (Huttunen *et al.*, 1987) and conventional electroencephalography (Macefield *et al.*, 1988*a*).

It has been argued that the compound EPSPs set up in soleus motoneurons by percussion on the Achilles tendon or by electrical stimulation of the tibial nerve in the popliteal fossa last so long (>10 ms, <5 ms, respectively) that contamination of the afferent volleys by cutaneous afferents could result in cutaneous inputs affecting the reflex discharge, particularly the ankle jerk (Burke *et al.*, 1983, 1984). This was considered less likely with the H reflex because it was calculated that the cutaneous volley would reach the motoneuron pool too late. On the basis of the present findings cutaneous volleys would reach the spinal cord at a similar time as muscle afferent volleys and only the length and excitability of the interneuronal chain would prevent their participation in determining the size of the H reflex. The present findings thus reinforce the need to be cautious in interpreting the results of studies that have used the H reflex as a purely monosynaptic reflex to probe motoneuron excitability in human subjects.

Cutaneous mechanoreceptors are powerfully activated when the human hand performs a motor task (Hulliger *et al.*, 1979; Westling and Johansson, 1987; Burke *et al.*, 1988), perhaps as much so as intramuscular mechanoreceptors, and the afferent volleys so generated have similar conduction velocities (present study). Classical teachings have assigned a purely perceptual role to cutaneous afferents, denying them a role in motor control, and a purely motor role to muscle mechanoreceptors, denying them a role in conscious sensation. There is increasing evidence that the former view is as untenable as the latter. In the human hand, low-threshold cutaneous afferents from the digits influence the excitability of the muscles acting on the digits via a spinal pathway (e.g., Jenner and Stephens, 1982; Aniss *et al.*, 1988), and tactile afferents from the finger tips have been shown to be crucial for adjusting the forces generated by the muscles involved in maintaining precision grip of an object (Johansson and Westling, 1987; Westling and Johansson, 1987).

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THE ROLE OF THE SUBTHALAMIC NUCLEUS IN EXPERIMENTAL CHOREA

EVIDENCE FROM 2-DEOXYGLUCOSE METABOLIC MAPPING AND HORSERADISH PEROXIDASE TRACING STUDIES

by I. J. MITCHELL, A. JACKSON, M. A. SAMBROOK
and A. R. CROSSMAN

(From the Experimental Neurology Group, Department of Cell and Structural Biology, School of Biological Sciences, University of Manchester, Manchester, UK)

SUMMARY

In previous studies we have shown that hemichorea can be induced in the conscious monkey by localized injection of gamma-aminobutyric acid (GABA) antagonists into the contralateral lentiform complex. It has been argued that the primary site of drug action in inducing chorea is the lateral segment of the globus pallidus. In the present study, the neural mechanisms which underlie this experimental dyskinesia were investigated by two separate approaches. First, the efferent projections of the lentiform complex were mapped using neuroanatomical tracing techniques. This involved injecting horseradish peroxide into sites which had previously given chorea when injected with the GABA antagonist bicuculline. Secondly, the 2-deoxyglucose (2-DG) metabolic mapping technique was applied to animals during active dyskinesia. This procedure permitted the autoradiographic measurement of local cerebral glucose uptake which was used as an index of regional synaptic activity. In both instances, the strongest labelling was seen in the dorsolateral region of the subthalamic nucleus. On the basis of this finding it is suggested that the pallidosubthalamic pathway plays a crucial role in the mediation of experimentally-induced chorea. Specifically, the pallidosubthalamic pathway arising from the lateral pallidal segment is abnormally overactive, which causes physiological inhibition of the subthalamic nucleus. The pattern of 2-DG uptake in the medial segment of the globus pallidus and thalamus was similar to that seen in animals with experimentally-induced ballism. This similarity is interpreted as suggesting that a common neural mechanism underlies both experimentally-induced chorea and ballism.

INTRODUCTION

In previous reports we have demonstrated that choreic movements of the contralateral limbs and/or face could be elicited in the conscious monkey by the injection of the gamma-aminobutyric acid (GABA) antagonist, bicuculline, into the contralateral lentiform complex (Jackson and Crossman, 1984). An extensive mapping study has been conducted in order to define the nature of the dyskinesia and to define the regions from which the choreic movements could be provoked (Crossman *et al.*, 1988).

Injection sites from which dyskinesia could be evoked were found predominantly in

Correspondence to: Professor A. R. Crossman, Department of Cell and Structural Biology, School of Biological Sciences, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK.

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the medial putamen and the lateral segment of the globus pallidus. Positive sites were also occasionally found in the substantia innominata and amygdala. The most sensitive sites lay near the lateral medullary lamina which separates the lateral pallidal segment from the putamen.

The interpretation placed on these studies was that the primary site of action of GABA antagonists in inducing dyskinesia was the lateral pallidal segment. Dyskinesia provoked by injections outside the confines of the lateral pallidal segment were thought to be due to diffusion of drug to this structure. It was hypothesized that antagonism of GABA caused blockade of the striatopallidal GABAergic projection from the cells of the putamen to the lateral pallidal segment. This would cause disinhibition of the neurons of the lateral pallidal segment which in turn project inhibitory fibres onto the subthalamic nucleus (Ohye *et al.*, 1976; Kita *et al.*, 1983). It was hypothesized that physiological inhibition of the subthalamic nucleus by overactivity in the lateral pallidal segment underlies this form of experimental chorea and possibly manifestations of the condition in man, such as that seen in Huntington's disease. Since loss of subthalamic activity is well known to underlie the appearance of ballism both in man and experimentally in the monkey (Whittier, 1947; Whittier and Mettler, 1949; Crossman, 1987) it was proposed that common neural mechanisms underlie ballism and chorea.

Further insight into the mechanisms that underlie dyskinesia have been gained by the use of the 2-deoxyglucose (2-DG) mapping technique. This procedure utilizes tritium-labelled 2-DG, an analogue of glucose, which is administered to animals during active dyskinesia. The regional uptake of 2-DG can then be visualized by autoradiography and quantified by densitometric techniques. Differential isotopic labelling between regions indicates differences in metabolic activity and thus, by implication, of neuronal electrical activity (Sokoloff *et al.*, 1977).

2-DG studies in experimental ballism (Mitchell *et al.*, 1985) induced by injection of GABA antagonists into the subthalamic nucleus have indicated that the mechanism involved in the production of dyskinesia is loss of excitation of the globus pallidus by the subthalamic nucleus. This leads to decreased activity of the neurons projecting from the medial segment of the globus pallidus to target nuclei such as the ventral thalamic nuclei.

The present studies were designed to test the model of chorea previously proposed and to further elucidate the neural mechanisms underlying dyskinesia. Two experimental approaches were employed. The first entailed injection of the neuroanatomical tracer, horseradish peroxidase (HRP), into sites from which chorea had been elicited following injection of bicuculline on a previous occasion. The brains were subsequently processed for HRP histochemistry and examined for anterograde transport of the tracer. This technique enabled the efferent projections of the area injected to be visualized and thus revealed the possible pathways by which the dyskinesia was mediated. A second experimental approach was then adopted in an attempt to demonstrate which of these efferent projections were primarily involved in the mediation of the dyskinesia. This involved the application of the 2-DG uptake technique to animals during active dyskinesia.

The results of the experiments reported in this paper add further support to the hypothesis that disordered activity of a common neural mechanism underlies chorea and ballism. The possibility of the existence of functional heterogeneity within the pallidosubthalamic pathway is also discussed.

MATERIAL AND METHODS

Animals and surgical procedures

The HRP tracing and 2-DG experiments were performed on 8 female monkeys (4 Macaca fascicularis; CYN104, 105, 108, 109 and 4 Macaca nemestrina; PTM B, F, K, L) weighing 3–5 kg. The lentiform complex of all animals was cannulated in order to permit the intracerebral injection of GABA antagonists.

The animals were anaesthetized with ketamine hydrochloride (15 mg/kg) and xylazine (3.0 mg/kg) administered intramuscularly (i.m.), and supplemented as necessary. All surgical procedures were performed taking aseptic precautions.

In order to improve stereotactic accuracy, x-ray ventriculography was performed, the details of which are described in full elsewhere (Crossman *et al.*, 1984). In brief, approximately 1 ml Omnipaque contrast medium (Nyegaard) was injected into the lateral ventricle and lateral radiographs taken against a graduated radio-opaque reference scale. These were then compared with standard atlases and estimates made of the corrections required to enable accurate placement of the intracerebral cannulae.

Under general anaesthesia, stainless steel cannula guides were inserted into the brain under stereotactic control, and secured to the skull using stainless steel screws and dental acrylic cement. The cannula guides consisted of a guide tube (0.46 mm o.d. and 0.25 mm i.d.) attached to a base, the latter being located on the surface of the skull to serve as anchorage for the cement. When not in use, the cannula guide contained a blank which bore a stainless steel stylette (0.23 mm diameter) to ensure patency of the guide tube (Needham *et al.*, 1983).

Drug injection

In order to make intracerebral drug injections, the animal was lightly anaesthetized with ketamine, administered i.m. The central blank was removed from the cannula guide and replaced with a mechanically operated micropump, which contained either a solution of bicuculline methiodide in sterile saline (15 μg/μl) or vehicle alone. The pump bore an injection needle (0.20 mm diameter) which passed through the guide tube and into the structure to be injected.

The construction and operation of the pump have been described in detail elsewhere (Needham *et al.*, 1983). The animal was allowed to recover fully from anaesthesia, and the pump was then triggered to deliver a volume of 2 μl. Animals were observed for a minimum of 1 h after injection and any abnormalities of movement recorded on film or videotape.

HRP procedure

In 2 animals (PTM B and F), injections of HRP (Sigma grade VI, 0.1 μl, 30% aqueous) were made bilaterally via a Hamilton syringe into sites where injection of bicuculline had previously given rise to choreic movements. Animals were then allowed to survive for 2 days, after which they were anaesthetized with ketamine. A lethal dose of barbiturate was then administered and the animals perfused transcardially with 0.9% saline, followed by an aldehyde fixative (after Mesulam, 1978). The brains were removed and frozen sections cut at 20–40 μm. Alternate series of sections were processed for HRP using the tetramethylbenzidene technique (after Mesulam, 1978), or to demonstrate the location of injection sites using cresyl violet.

2-deoxyglucose methods

The 2-DG procedure was performed on 5 of the animals (PTM K and L; CYN 104, 105 and 108) once the bicuculline injection had elicited chorea, in accordance with the protocol described elsewhere (Mitchell *et al.*, 1985). Briefly this procedure involved injecting 5 mCi tritiated 2-DG (New England Nuclear) i.v. once clear signs of dyskinesia were evident. After 45 min the monkey was killed by barbiturate overdose and the brain was quickly frozen in situ in isopentane at −40° C. The brain was exposed by careful drilling and then sectioned by cryostat; 20 μm sections were thaw-mounted onto gelatinized microscope slides and immediately refrozen. The sections were then freeze-dried and loaded into x-ray cassettes with LKB Ultrofilm. Following an exposure period of approximately 25 days the autoradiographs were developed in Kodak D19, fixed in Kodafix, and analysed densitometrically using a Seescan Solitaire image analysis system (Seescan, Cambridge, UK). The parent sections were stained with cresyl violet for histological examination.

The sixth monkey served as a control and received an injection of saline into the lentiform complex at a site from which chorea could be elicited by injection of a similar volume of bicuculline solution. The animal then received an injection of 2-DG and was treated in exactly the same manner as the other animals.

Analysis of 2-DG data

For each structure examined, readings were taken bilaterally from at least 6 different autoradiographs and these data were used to calculate the mean percentage side-to-side change in relative optical density which resulted from the bicuculline injection. In addition, the mean optical density readings of the structures ipsilateral to the injection were statistically compared with the equivalent contralateral structures using matched paired t tests. The optical density scores from the control animal were treated in a similar manner.

The percentage side-to-side changes in 2-DG uptake in the control animal were also compared with the distribution of equivalent values for the choreic animals. This comparison served to indicate whether the changes in 2-DG uptake seen in the choreic animals were due to the dyskinetic state or due to the nonspecific action of injecting a substance into the lentiform region. Changes in 2-DG uptake were considered to be due to the experimental manipulation whenever the mean percentage side-to-side differences in the choreic animals differed from the control scores by at least 2 SEM.

RESULTS

Nature of the movement disorder

The injection of bicuculline methiodide into the ventral lentiform complex resulted in a choreiform dyskinesia as described elsewhere (Crossman *et al.*, 1988). The pattern of dyskinesia observed in CYN 104 was typical of the group, and is described in detail.

Within 3 min of the bicuculline injection equivocal abnormal movements were seen in the contralateral upper and lower limb; 5 min after the injection, abnormal flexion/extension movements of the foot could clearly be seen. The severity of these movements increased and by 10 min postinjection the hip, knee and ankle were all involved in abnormal movements. 2-DG was administered 70 min after the bicuculline injection at which stage the chorea was unambiguous and persistant. During the 45 min period of 2-DG uptake the dyskinesia was characterized by abduction/adduction of a flexed hip combined with flexion/extension at the knee, ankle and toes. These movements were often almost ballistic in nature, and continuous. The upper limb was affected to a lesser extent, and displayed intermittent choreic movements. A similar pattern of abnormal movements was seen in all the animals with the following exceptions.

CYN 108 showed mild myoclonic movements of the contralateral upper limb in addition to pure choreic movements of the lower limb. The choreic movements seen in PTM K and PTM L were not as severe as those seen in the other animals and were more intermittent. The latency of onset of chorea in these 2 animals was also longer, choreic movements first being seen 15 min after the bicuculline injection and only becoming marked after a further 30 min. The injection of saline in the control animal gave rise to no abnormal movements.

Verification of injection sites

The precise location of the injection sites which gave rise to dyskinesia was determined by careful examination of the cresyl violet-stained sections. Injections of both bicuculline and HRP were centred in the lateral pallidal segment or medial part of the putamen in precisely the region previously shown to be the most sensitive basal ganglia site for the production of dyskinesia with GABA antagonism (Crossman *et al.*, 1988).

The precise location of the bicuculline injection sites in the 2-DG animals are shown

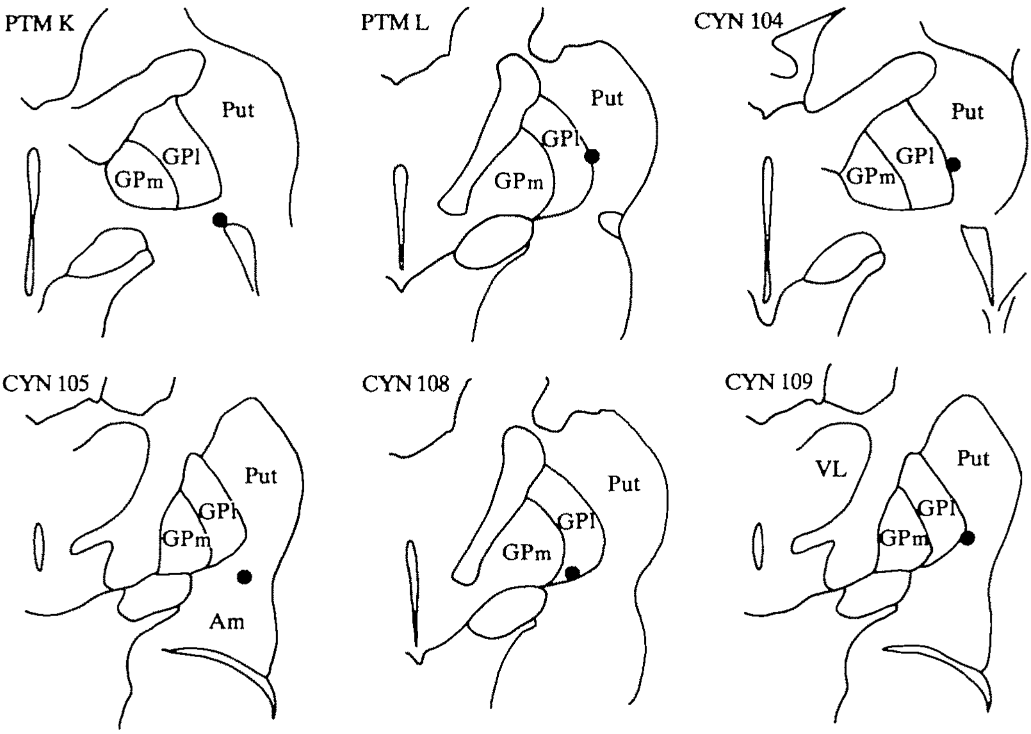

FIG. 1. Locations of bicuculline injection sites in the 5 experimental animals and the saline injection site in the control animal (CYN 109). Abbreviations: Am = amydaloid complex; GPm = medial segment of the globus pallidus; GPl = lateral segment of the globus pallidus; Put = putamen; VL = ventral lateral nucleus of the thalamus.

in fig. 1. The injection in CYN 108 was located in the ventral portion of the lateral pallidal segment. The injection in CYN 105 was centred beneath the lentiform complex at the border of the lateral amygdaloid nucleus, basolateral amygdaloid nucleus, substriatal grey and basal nucleus of Meynert. PTM K also received an injection which was centred in the lower part of the lentiform complex. CYN 104 and PTM L both received injections in the medial aspect of the ventral putamen where the nucleus borders the lateral pallidal segment. The injection of saline in the control animal, CYN 109, was similarly placed on the border of the putamen and lateral pallidal segment.

The bicuculline injection sites in the animals which received HRP were all centred on the ventromedial putamen, adjacent to the lateral pallidal segment.

Results of HRP tracing experiments

In all cases the HRP injection was centred in the ventromedial putamen, though significant spread to the adjacent lateral pallidal segment was seen. A consistent pattern of both anterograde and retrograde transport of HRP resulting from each of these injections was clearly visible.

The heaviest terminal labelling was seen in the ipsilateral subthalamic nucleus. This labelling was highly heterogeneous. Dense labelling was seen in the dorsolateral third

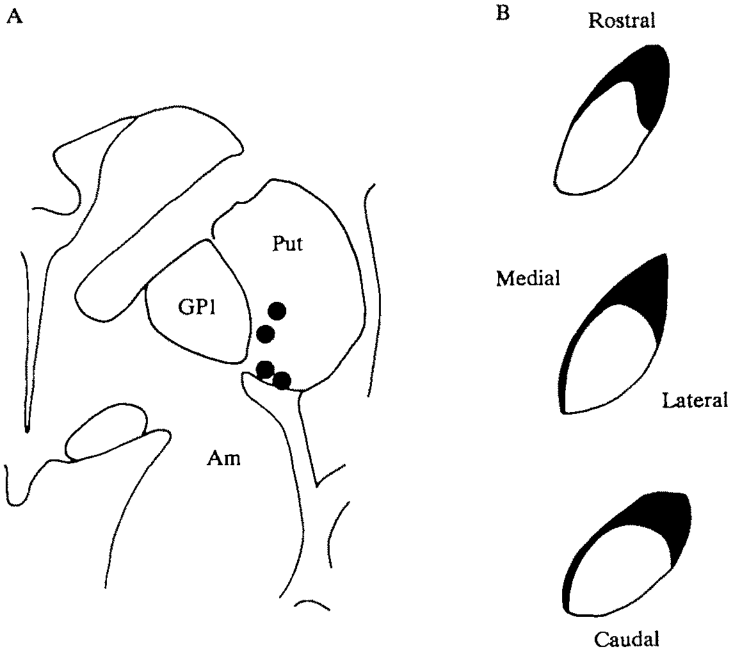

FIG. 2. Results of the HRP tracing experiment. A, distribution of sites which elicited chorea when injected with bicuculline and which were subsequently injected with HRP. All these injections gave a very similar pattern of anterograde transport of HRP, the heaviest terminal label being seen in the subthalamic nucleus. B, composite picture of terminal label in the subthalamic nucleus based on all four injections. Abbreviations as in fig. 1.

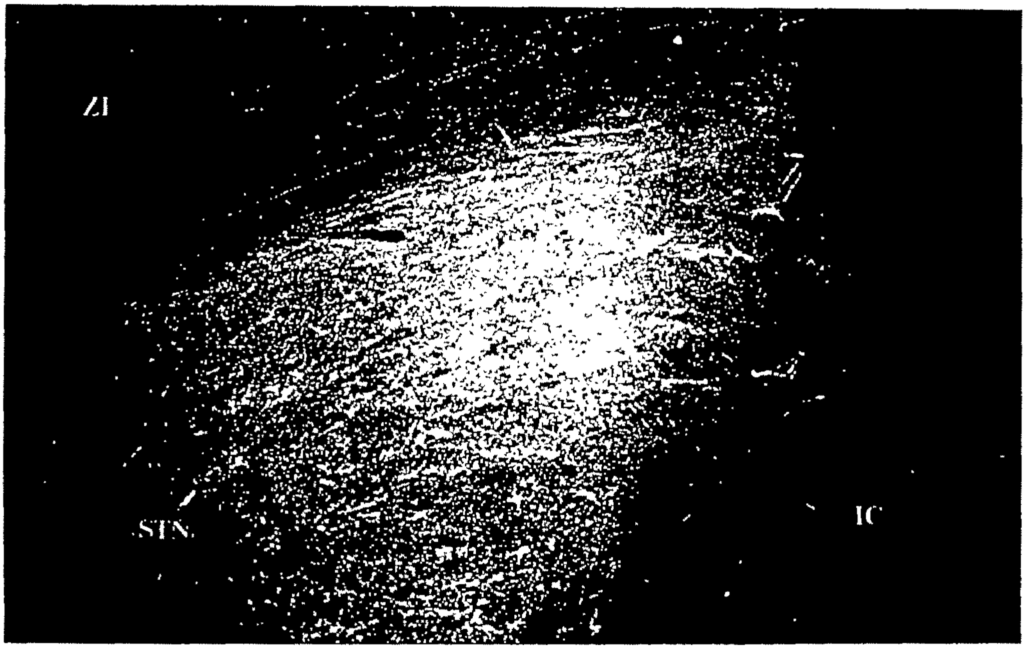

FIG. 3. Photomicrograph of the dorsolateral tip of the right subthalamic nucleus following an injection of HRP into the ipsilateral ventral lentiform complex. Note the anterograde labelling in the dorsolateral portion of the nucleus. Abbreviations: STN = subthalamic nucleus; ZI = zona incerta; IC = internal capsule.

and along the dorsal border of the nucleus whereas the remainder of the structure was free of any label. This is illustrated in figs 2 and 3. Anterograde labelling of terminal fields was also observed in several other structures including the globus pallidus, substantia nigra pars reticulata and pedunculopontine nucleus of the caudal midbrain.

Within the globus pallidus the label was restricted to the ventral parts of both segments. Terminal labelling in the substantia nigra pars reticulata lay in bands, perpendicular to the cerebral peduncle, with unlabelled areas between them. These bands of terminal labelling were seen to lie next to bands of retrogradely labelled substantia nigra pars compacta neurons (*see below*).

Retrogradely-labelled neurons were observed in the cerebral cortex and in the lateral third of the subthalamic nucleus in all cases. Numerous labelled neurons were observed in the centromedian nucleus of the thalamus, in the dorsal raphe nucleus and in the pedunculopontine nucleus.

In the ventral mesencephalon, heavy retrograde transport labelling was seen in both the substantia nigra pars compacta and the ventral tegmental area (VTA). This labelling was organized topographically and was similar in all cases. Labelled neurons were located predominantly in the lateral third of the substantia nigra pars compacta at its anterior pole. However, at more caudal levels, labelled neurons were seen to lie in bands running from medial to lateral within the VTA, extending as far medially as the fibres of the third nerve.

TABLE 1. DENSITOMETRIC ANALYSIS OF THE CONTROL ANIMAL WHICH RECEIVED A SALINE INJECTION INTO THE VENTRAL LENTIFORM COMPLEX SHOWING THE OPTICAL DENSITIES FOR EACH STRUCTURE ON BOTH THE INJECTED AND UNINJECTED SIDES OF THE BRAIN AND THE PERCENTAGE INCREASE IN OPTICAL DENSITY OF THE INJECTED OVER THE UNINJECTED SIDE

	Uninjected side	*Injected side*	*Percentage increase in optical density*
Caudate nucleus	0.2861	0.2856	−0.17
Putamen	0.2697	0.2549	−5.48
Medial pallidal segment	0.2932	0.2870	−2.10
Lateral pallidal segment	0.2737	0.2602	−4.93
Subthalamic nucleus	0.4102	0.4091	−0.27
Substantia nigra pars reticulata	0.3118	0.3212	+3.01
Ventral anterior nucleus of the thalamus	0.3327	0.3241	−0.92
Ventral lateral nucleus of the thalamus	0.2968	0.2857	−1.11
Centromedian-parafascicular complex	0.3273	0.3304	+0.95

TABLE 2. 2-DG DENSITOMETRIC ANALYSIS OF THE 5 ANIMALS IN WHICH A CHOREIC SYNDROME WAS INDUCED BY THE INJECTION OF BICUCULLINE INTO THE VENTRAL LENTIFORM COMPLEX

	Uninjected side	*Injected side*	*Mean percentage increase*
Caudate nucleus	0.4905±0.055	0.4813±0.058	−1.91±1.34
Putamen	0.4639±0.047	0.4638±0.050	−0.02±2.14
Medial pallidal segment	0.2911±0.039	0.2718±0.045*	−6.68±2.04
Lateral pallidal segment	0.2597±0.032	0.2870±0.045*	10.2±3.13
Subthalamic nucleus	0.3973±0.052	0.4489±0.078**	12.6±2.24
Substantia nigra pars reticulata	0.3219±0.040	0.3282±0.036	2.12±1.04
Vental anterior nucleus of the thalamus	0.3179±0.028	0.3099±0.024*	−2.42±0.72
Ventral lateral nucleus of the thalamus	0.3046±0.046	0.2940±0.045*	−3.47±0.88
Centromedian-parafascicular complex	0.3464±0.045	0.3587±0.042*	−2.18±0.44

For each structure the mean optical density score for the uninjected and injected sides are shown. Numbers are mean and standard errors. Matched pair t tests were used to compare the uninjected and injected optical density values; $^*P < 0.05$, $^{**}P < 0.01$. The mean percentage increase in optical density of the injected side over the uninjected side for each structure is also shown ±SEM.

Results of 2-DG autoradiography

The results of the densitometric analysis of the control animal showed small side-to-side differences in 2-DG uptake. These were expressed in terms of percentage differences and are shown in Table 1. The results of the densitometric analysis of the experimental

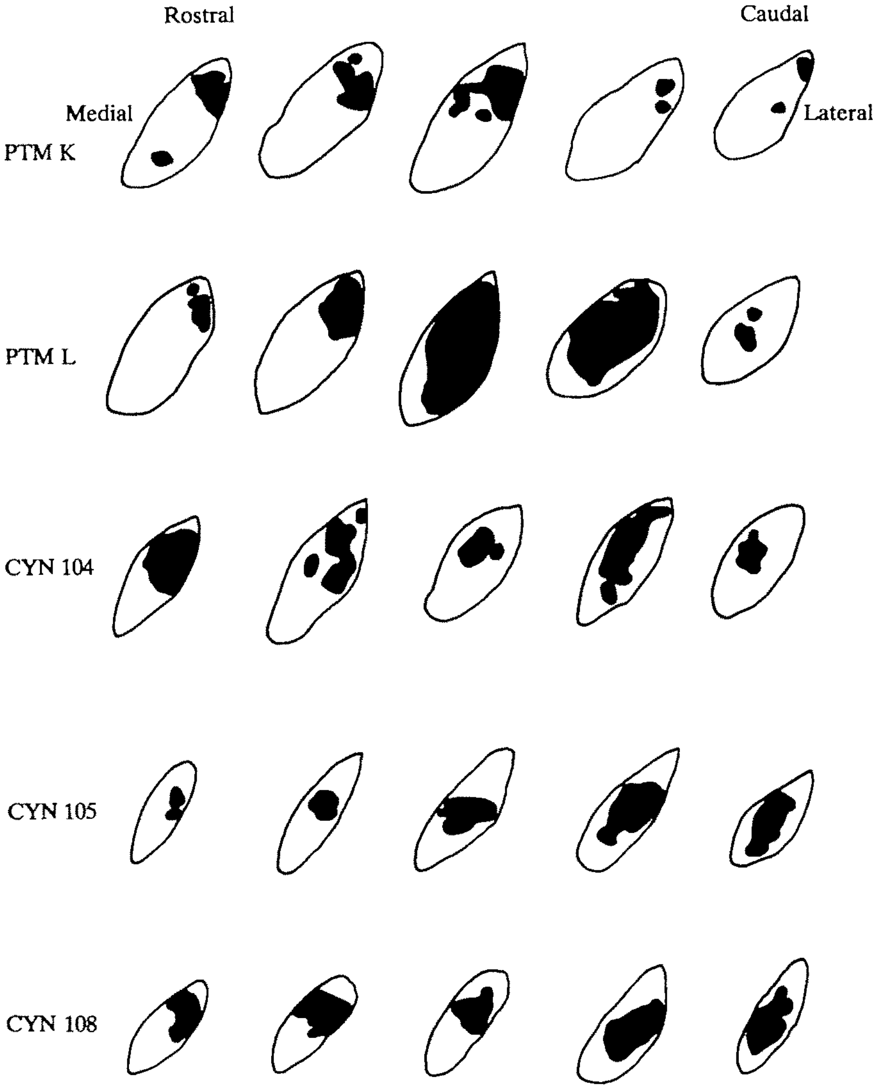

FIG. 4. Diagram showing the results of the threshold analysis of 2-DG uptake in the subthalamic nucleus. The subthalamic nucleus ipsilateral to the bicuculline injection is shown at 5 different rostrocaudal levels in each of the 5 experimental animals. In each case, the stippled area represents a region of increased 2-DG uptake relative to the equivalent position in the contralateral structure.

animals are shown in Table 2. The pattern of 2-DG uptake is described in each structure examined.

Striatum. Analysis of the autoradiographs showed the distribution of 2-DG uptake in the caudate nucleus on both the injected and uninjected sides of the brain to be homogeneous. A small nonsignificant decrease in optical density was seen in the caudate nucleus ipsilateral to the injection compared to the contralateral side (1.91%). Similarly, the ipsilateral putamen showed a small, nonsignificant decrease in optical density, (0.02%).

Globus pallidus. The lateral segment of the globus pallidus ipsilateral to the injection showed a significant increase in optical density of 10.2% compared with the control side. In contrast, the ipsilateral medial segment of the globus pallidus showed a significant decrease in optical density of 6.86% compared with the contralateral side.

Substantia nigra. The ipsilateral substantia nigra pars reticulata showed a small nonsignificant increase in optical density of 2.12%.

Subthalamic nucleus. The subthalamic nucleus showed the largest change in optical density of any brain structure. When the nucleus was analysed as a whole it was found to have a significantly increased uptake of 2-DG of 12.6%. However, the distribution of labelling was far from homogeneous. The majority of the increase in 2-DG uptake was located in the dorsolateral portion of the nucleus. This was subsequently analysed in detail by means of a threshold analysis.

This procedure entailed setting a threshold which corresponded to a specific optical density, in this instance the optical density of the control subthalamic nucleus (i.e., contralateral to the bicuculline injection). The ipsilateral subthalamic nucleus was then examined using this threshold. Only areas which were above this threshold, i.e., more optically dense than the control structure, appeared in the final image.

The results of this analysis are shown in fig. 4. The outline of the subthalamic nucleus from each animal is shown at 5 different rostrocaudal levels. The filled area corresponds to the region of increased uptake of 2-DG. As can be seen, the area of increased uptake was generally located within the dorsal two-thirds of the nucleus, though the actual dorsal tip of the structure was only affected in 1 animal (PTM L). In contrast, the ventromedial portion was rarely affected. This pattern of 2-DG uptake was present throughout the whole of the rostrocaudal extent of the structure.

Thalamus. The ventral anterior nucleus of the thalamus ipsilateral to the injection of bicuculline showed a decrease in optical density of 2.42% compared with the control side whereas the ventral lateral nucleus showed a decrease of 3.47%. The centromedian-parafascicular complex also showed a modest but significant decrease in optical density of 2.18%.

DISCUSSION

Experimental chorea

The results of this study demonstrated that injection of GABA antagonists into the lentiform complex can elicit dyskinesia as previously described (Crossman *et al.*, 1988). The dyskinesia was typically manifested as choreic movements which involved the proximal and distal musculature of the contralateral upper and lower limb. The location of the bicuculline injection sites was found to vary though all were located in or near the ventral part of the lentiform complex.

Distribution of anterogradely-transported HRP

Injections of HRP into the ventral lentiform complex resulted in the anterograde transport of the tracer to several structures including the medial pallidal segment, the subthalamic nucleus, the substantia nigra pars reticulata, the centromedian-parafascicular complex of the thalamus, and the pedunculopontine nucleus. Thus each of these areas may represent a region of termination of the efferent projections from the ventral lentiform area. The heaviest labelling and most consistent label was seen in the subthalamic nucleus regardless of the precise site of the injection. Furthermore, the distribution of anterograde HRP label within the subthalamic nucleus was not homogeneous, the labelling being restricted to the dorsolateral third and dorsal border of the nucleus.

This labelling is most likely due to uptake of the enzyme by neurons in the lateral pallidal segment and transportation along the pallidosubthalamic pathway to terminals in the subthalamic nucleus. This interpretation is supported by the evidence relating to the topography of the pallidosubthalamic projection, certain features of which have been previously reported. Thus it has been demonstrated that neurons in the central portion of the lateral pallidal segment project to the lateral third of the subthalamic nucleus throughout most of its rostrocaudal extent in the monkey (Carpenter *et al.*, 1981*a, b*).

This reliable labelling of the pallidosubthalamic pathway, independent of the precise location of the injection site within the region of the lentiform complex, is compatible with the hypothesis that this pathway probably plays a critical role in the mediation of the chorea induced by this experimental procedure. This suggests that although injections of bicuculline into the structures which surround the lentiform nucleus, such as the amygdala and substantia innominata, are capable of producing chorea, it is the disruption of GABAergic transmission within the lateral pallidal segment which is the critical factor for eliciting the movement disorder. This evidence is in accordance with the predicted mechanism of experimental chorea previously presented (Crossman *et al.*, 1988).

Regional distribution of 2-DG uptake

Significant side-to-side changes in optical density were seen in the autoradiographs of the subthalamic nucleus, medial pallidal segment, ventral anterior and ventral lateral nuclei of the thalamus and the centromedian nucleus-parafascicular complex, the pattern of labelling being largely independent of the exact location of the site of injection. For all these structures, with the exception of the lateral pallidal segment, the mean percentage score deviated from the equivalent score in the control animal by at least 2 SEM. Since these side-to-side differences were greater than those seen in the control animal it is concluded that the asymmetries are due to the expression of the dyskinesia and not an artefact of the injection procedure. The side-to-side change in optical density seen in the lateral pallidal segment of the experimental animals was significant, although it was of a similar magnitude to that seen in the control animal. This probably reflects a nonspecific effect of the injection cannula which passed through the structure.

Neural mechanisms underlying regional changes in 2-DG uptake

The changes in 2-DG uptake that occur following an experimental manipulation probably reflect changes in the overall level of synaptic activity within a structure rather than a change in the firing rate of the neuron cell bodies which it contains (Schwartz *et al.*, 1979; Mata *et al.*, 1980; Auker *et al.*, 1983). Thus changes in the discharge frequency of a neuron are reflected in changes in the optical density of its projection areas rather than in the structure itself. Consequently, the side-to-side changes in the optical density seen in the experimental animals are interpreted as being due to changes in synaptic activity.

In all 5 experimental animals the subthalamic nucleus ipsilateral to the injection showed a dramatic increase in 2-DG uptake irrespective of the precise location of the injection site. The most likely explanation for this result is that the expression of chorea was associated with an increase in the activity of the afferent inputs to the subthalamic nucleus. The most likely candidate for this would be the lateral pallidal segment which, as demonstrated by the HRP studies, sends a massive topographically organized projection to the subthalamic nucleus.

This hypothesis is attractive in the light of the close correspondence of the pattern of 2-DG uptake and distribution of HRP label within the subthalamic nucleus. Thus in all of the 2-DG animals the dorsolateral part of the nucleus was predominantly affected although the actual dorsal tip rarely showed an increase in labelling, irrespective of the exact location of the injection site. All of the rostrocaudal extent of the nucleus was affected, although in more caudal regions the affected area moved more ventrally. Thus although the correlation between the pattern of labelling of HRP and 2-DG was not identical, there was considerable overlap. This close correspondence between the two types of labelling in the subthalamic nucleus reinforces the hypothesis that it is altered transmission in the pallidosubthalamic pathway which is critical for the production of choreiform movements.

The pallidosubthalamic pathway is thought to utilize the inhibitory transmitter GABA (Ohye *et al.*, 1976; Kita *et al.*, 1983). Accordingly, increased activity in this pathway would be expected to result in a reduction in the activity of neurons of the subthalamic nucleus. This probably represents the prime pathway for the mediation of the dyskinesia.

The subthalamic nucleus in turn projects to both pallidal segments and the substantia nigra pars reticulata (Nauta and Cole, 1978). The medial pallidal segment showed a consistent decrease in 2-DG uptake, implying that the input from the subthalamic nucleus was indeed underactive. The medial pallidal segment projects to ventral anterior, ventral lateral and centromedian nuclei of the thalamus (Nauta and Mehler, 1966; Kim *et al.*, 1976; DeVito and Anderson, 1982), all of which showed decreases in 2-DG uptake. By the same reasoning it would appear that the medial pallidal segment is also underactive during experimentally-induced chorea. This interpretation is in keeping with current opinions on the nature of the transmitter released by the subthalamic nucleus which, on the basis of immunohistochemical, electrophysiological and behavioural data, is thought to be the excitatory amino acid, glutamate (Kitai and Kita, 1987; Smith and Parent, 1988; Robertson *et al.*, 1989).

The role of the pallidosubthalamic pathway in the mediation of chorea

The hypothesis that bicuculline acts primarily on the lateral pallidal segment in eliciting chorea is also in keeping with current hypotheses concerning the pathophysiology of the choreic movements seen in Huntington's disease. The pathology of this disease is characterized by the loss of striatopallidal and striatonigral GABAergic projection fibres (Bruyn, 1968; McGeer *et al.*, 1973; Perry *et al.*, 1973; Bird and Iversen, 1974; McGeer and McGeer, 1976; Gale *et al.*, 1978). Recent evidence has demonstrated that the degeneration of the striatal output cells proceeds at differential rates. The cells which project to the lateral pallidal segment in which enkephalin is colocalized appear to be lost first, their degeneration correlating well with the appearance of the choreic symptoms. The cells which project to the medial pallidal segment and substantia nigra in which substance P is colocalized are lost only in the later stages of the disease, the degeneration being temporally correlated with the appearance of dystonic symptoms (Reiner *et al.*, 1988). Thus it would be predicted that the chorea associated with Huntington's disease arises because of the loss of inhibition of lateral pallidal cells. Accordingly, the pharmacological blockade of the striatal projection to the lateral pallidal segment in the monkey would be expected to result in a similar dyskinesia.

If the mechanism of chorea presented here proves to be correct, increased activity of the pallidosubthalamic pathway would result in decreased activity of the subthalamic nucleus. This would be in keeping with the well-established observation that lesions of the subthalamic nucleus, in both man and monkey, give rise to ballism (Whittier, 1947; Whittier and Mettler, 1949; Crossman, 1987) and would explain the striking similarity between the physical characteristics of dyskinesia induced by subthalamic and pallidal manipulation. Furthermore, this would suggest that chorea and ballism share a common neural mechanism.

It is interesting to speculate on whether other forms of movement disorder are also mediated by disordered activity in the same neural pathways. Evidence from 2-DG studies of MPTP-treated monkeys suggest that this may indeed be the case for parkinsonism (Crossman, 1987). In 2-DG autoradiographs from parkinsonian animals given the neurotoxin MPTP, the subthalamic nucleus consistently showed a dramatic change in optical density compared with control values. However, in these animals the subthalamic nucleus showed a decrease in 2-DG uptake, suggesting that experimental parkinsonism is characterized by underactivity in the pallidosubthalamic pathway. Whether or not this pathway is critically involved in the mediation of other forms of dyskinesia such as levodopa-induced chorea and tardive dyskinesia is the subject of on-going experiments.

Functional heterogeneity within the subthalamic nucleus

The finding that only a restricted portion of the subthalamic nucleus showed abnormal 2-DG uptake during experimentally-induced chorea suggests that this structure may be heterogeneously organized with respect to function. Support for such a concept can be found in the electrophysiological studies of DeLong *et al.* (1985) who have demonstrated in unit recording experiments in behaving primates that cells related to movements of different body parts are differentially located in this nucleus. Similarly, Parent and Smith (1987) have demonstrated that the outputs of the subthalamic nucleus are heterogeneously organized. Thus the different efferent projections of the subthalamic nucleus arise from cells located in different parts of the structure. The dorsolateral 80% of the structure contains cells which project to the globus pallidus, whereas the cells which project to the substantia nigra pars reticulata are found in the ventral 20%.

In the experiments reported here, the labelling of the subthalamic nucleus which resulted from both the HRP injections and as a result 2-DG administration both seem to avoid the ventromedial 20% of the structure. It is thus tempting to speculate that the part of the subthalamic nucleus which projects to the substantia nigra pars reticulata is less involved in the mediation of experimentally-induced chorea than the dorsolateral part which projects to the globus pallidus. This hypothesis is supported by the failure to find a significant change in 2-DG uptake in the substantia nigra pars reticulata in the experimental animals.

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LEXICAL AGRAPHIA IN THE JAPANESE LANGUAGE

PURE AGRAPHIA FOR KANJI DUE TO LEFT POSTEROINFERIOR TEMPORAL LESIONS

by YOSHIAKI SOMA,[1] MORIHIRO SUGISHITA,[1] KOICHI KITAMURA,[2] SHOICHI MARUYAMA[3] *and* HIROHISA IMANAGA[4]

(*From the* [1]*Department of Clinical Neurology, Tokyo Metropolitan Institute for Neurosciences, Departments of* [2]*Neurosurgery and* [3]*Neurology, Tokyo Women's Medical School, and* [4]*Department of Neurosurgery, Shiseikai Daini Hospital, Japan*)

SUMMARY

A new syndrome of 'pure agraphia for Kanji' is described in 3 Japanese subjects with lesions in the left posteroinferior temporal region. Kanji (ideogram or morphogram) can be compared with orthographically irregular or ambiguous words in some European languages, since it is impossible to write Kanji characters unless each one of them is learned and memorized. In contrast, Kana (phonogram or syllabogram) words are comparable with orthographically regular words or nonsense words, because the Kana writing system depends on strict phonological rules (almost one-to-one correspondence between syllable and syllabogram). We conclude that 'lexical agraphia' reported in European languages can also be observed in the Japanese language where it is expressed as 'pure agraphia for Kanji'. 'Lexical agraphia' is a useful concept with general application regardless of language system.

INTRODUCTION

Two different types of writing strategy have been postulated in some Western languages such as English or French: the phonological and lexical writing routes. A selective disturbance of the former results in phonological agraphia (Shallice, 1981; Roeltgen *et al.*, 1983), where disruption of a phoneme-to-grapheme conversion system causes difficulty in writing pronounceable nonwords or unfamiliar words. In contrast, a selective disturbance of the lexical writing route produces lexical agraphia (Beauvois and Dérouesné, 1981; Croisile, 1987; Gonzalez Rothi *et al.*, 1987), in which disruption of a whole-word retrieval system causes difficulty in writing familiar words which are orthographically irregular or ambiguous. A word is 'orthographically irregular or ambiguous' when its orthography is not definitely determined by its phonology. The Japanese writing system has a characteristic feature in that it is composed of two entirely different categories of letters: Kanji or ideograms which are identical to Chinese letters, and Kana or phonograms which are more or less similar to the alphabets of European languages.

Correspondence to: Dr Yoshiaki Soma, Department of Neurology, Brain Research Institute, Niigata University, 1-754. Asahimachi-dori, Niigata City, 951 Japan.

* Present address: Department of Neurology, Brain Research Institute, Niigata University, Japan.

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Kana words can be spelt correctly so long as it is known how to write each Kana letter. On the other hand, it is impossible to write Kanji characters correctly unless each of them is learned and memorized. In other words, Kanji characters cannot be written solely on the basis of their phonetic values. Writing Kana words therefore depends more on the phonological writing system, while writing Kanji must depend more on the lexical writing system.

We report 3 cases with left posteroinferior temporal lesions who presented pure agraphia almost exclusively for Kanji. This symptom can be regarded as an equivalent of lexical agraphia in some European languages. Detailed study of this syndrome will greatly help the understanding of the brain mechanism for written language in Japanese subjects. Moreover, it will be of general value to postulate a 'universal' model of reading/writing (Coltheart *et al.*, 1987). 'Pure agraphia of Kanji' forms a sharp contrast to 'selective Kana agraphia' (Tanaka *et al.*, 1987) whose basic mechanism lies in the process of converting an acoustic word image into a Kana motor grapheme sequence. The significance of this syndrome is also stressed in the light of its usefulness in explaining the complexity of neuropsychological symptoms due to left temporo-occipital pathology.

KANJI AND KANA

The Japanese writing system is characterized by its simultaneous employment of two different categories of letters.

Kanji, literally meaning Chinese characters, conveys both phonetic and semantic values at the same time and corresponds linguistically to morphemes or words (Table 1). Kanji characters are often referred to as ideograms, because each of them represents some semantic value. Usually a Kanji character has more than two phonetic values; one is On-reading, another is Kun-reading. Some authors (e.g., Iwata, 1984) prefer to call them morphograms because there is no priority between their phonetic and semantic values.

TABLE 1. EXAMPLES OF KANJI AND KANA LETTERS

Kanji	Kana (hira-kana) pronunciation		Meaning
	On-reading	*Kun*-reading	
山	さ ん [sa] [n]	や ま [ja] [ma]	Mountain
桜	お う [o] [u]	さ く ら [sa] [ku] [ra]	Cherry blossom
魂	こ ん [ko] [n]	た ま し い [ta] [ma] [ʃi] [i]	Soul

Kana, in contrast to Kanji, was created in Japan approximately 1000 yrs ago by simplifying or disintegrating Kanji. Consequently Kana letters are far less complex than Kanji in their configurations except for a small number of exceptionally simple Kanji. Kana (Table 1) conveys an exclusively phonetic value, losing the semantic value of the original Kanji completely. As a linguistic unit, a Kana letter corresponds to a consonant-vowel syllable, or a mora in the strict sense. Accordingly a Kana letter may as well be termed a syllabogram (Iwata, 1984).

The most significant difference between Kana and European alphabets lies in the fact that the phonetic value of a Kana letter is fixed and identical with the precise name of that Kana letter, and does not depend on its position in words or sentences. For example, the Kana letter か (ka) is always pronounced as such wherever it is placed in a word. That is, as if 'cat' were pronounced (si: ei tei). Consequently, in the Kana writing system, phonology and orthography correlate completely with few exceptions.

There are 46 basic Kana letters and 2 diacritical marks, making up a total number of 71. The number of Kanji characters is much larger. During the 9 yrs of compulsory education, 881 Kanji characters are taught, and 1850 Kanji are recommended by the government for standard use, such as in newspapers and magazines. A well-educated Japanese can read and write several thousands of Kanji characters. A medium-sized dictionary contains about 10,000 Kanji characters. More than 40,000 are listed in the biggest dictionaries.

Any word or sentence could be written by employing Kana letters alone, but simultaneous use of Kanji and Kana is more convenient and appropriate. Kanji characters are used most often for expressing nouns, but roots of verbs, adjectives, and adverbs are also frequently written in Kanji. Kana is employed to express the rest of the writing.

Each Kanji character has more than two phonetic values which can be classified into On and Kun-reading. In On-reading the original Chinese way of pronounciation is retained, while Kun-reading derives from a Japanese word which shares the same meaning as a Chinese letter. Consequently Kun and On-reading are quite different phonetically (Table 1). In the Kanji system there are many homophones. For example, there are more than 40 different Kanji characters for the pronounciation of [sei].

CASE REPORTS

Case 1

A 71-yr-old right-handed executive suddenly complained of headaches and word-finding difficulty. Hypertension of moderate degree which had been detected several years before had been well controlled with antihypertensive drugs. As a university graduate, his reading and writing competence was very high. For a few days after the onset of the illness the patient could not read or write at all, but his spoken language was normal except for word-finding difficulties. According to the patient, auditory comprehension was completely intact.

Neurological examination 1 wk after onset disclosed anomia in confrontation naming, and alexia with agraphia; the remainder of the examination, including the visual fields and motor and sensory function, was normal. His spontaneous speech was fluent and well articulated, without paraphasia. Repetition of words and phrases was perfect. Comprehension of spoken language was intact, which was later confirmed

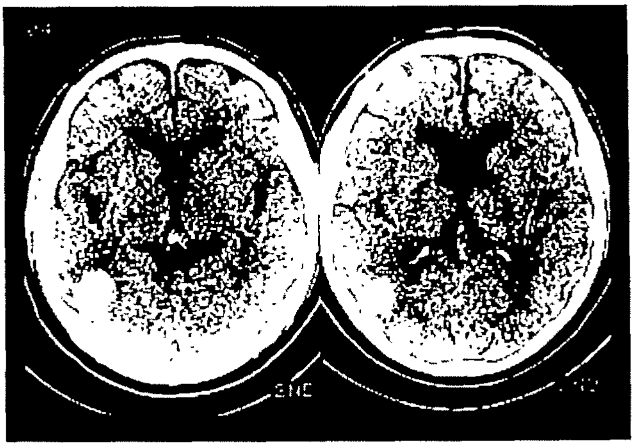

FIG. 1. CT scan from *Case 1* at 1 wk postonset showing an area of high density in the left posterior temporal region.

by the Token Test. CT studies 1 wk after the onset revealed a subcortical haematoma in the left posterior temporal region (figs 1, 4).

In the 2 wks after onset, the alexia disappeared gradually, enabling the patient to read newspapers and magazines without much difficulty. The agraphia, however, did not improve in parallel with the alexia, and he was unable to write anything other than his name, address, and the name of his company.

Four weeks after the onset the patient began to teach himself to write and found that he had far greater difficulty in writing Kanji than Kana. He himself observed that he could write nearly 100% of Kana letters but only about 50% of those Kanji characters which are in general use in newspapers and magazines. Word-finding difficulty began to improve at this time.

He returned to his previous occupation 6 mos after the onset with almost full competence except for writing tasks. Verbal IQ was 96, performance IQ 86, total IQ 93 on the Wechsler Adult Intelligence Scale, conducted 9 mos postonset.

Detailed neuropsychological studies were conducted 6 and 11 mos postonset.

Case 2

A 58-yr-old housewife visited the hospital because of word-finding difficulties. She had been in good health except for hypothyroidism and hypercholesterolaemia which were being treated medically. She had not progressed further than a 6-yr elementary school education, but she could read newspapers and magazines and she could write letters without much difficulty.

Neurological examination was normal except for anomia and alexia with agraphia. Spontaneous speech was fluent, well articulated, and without paraphasia, even though a notable deficiency in word-finding with frequent circumlocution was observed. For several days after the onset she could not even recall the names of her husband or children. Western Aphasia Battery testing demonstrated that repetition of words and phrases was normal, as was auditory comprehension. A CT scan showed infarction in the posterior portion of the left middle and inferior temporal gyri (figs 2, 4).

Detailed examinations in reading and writing were administered 4 wks and 4 mos postonset.

Case 3

A 36-yr-old right-handed engineer suffered severe head trauma as a result of falling from a roof. His level of consciousness fluctuated from somnolence to semicoma for a few wks. A CT scan revealed cerebral contusion and an intracerebral haematoma in the left temporal region with a shift of the midline structures

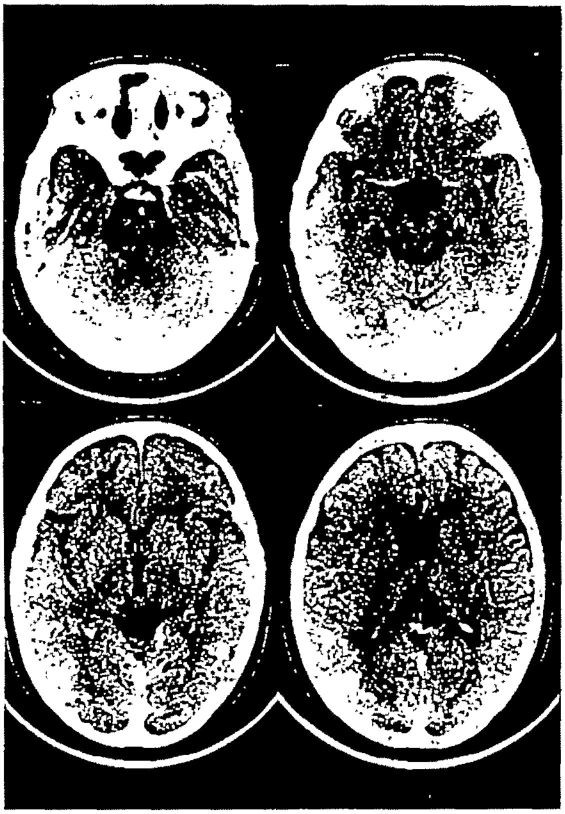

FIG. 2. Enhanced CT scan from *Case 2*, 18 days postonset. Contrast enhancement is seen in the left middle inferior and posteroinferior temporal areas.

to the right. One month after onset when the patient had regained full consciousness, anomia and alexia with agraphia were noted. The remainder of the neurological and neuropsychological examination was normal. A CT scan 2 mos after the onset demonstrated that the haematoma had completely disappeared and a low density area was present in the left posteroinferior temporal region (figs 3, 4).

Detailed neuropsychological examinations were conducted 2 and 9 mos postonset.

NEUROPSYCHOLOGICAL STUDIES

Methods

In order to evaluate reading and writing competence qualitatively, we employed either a set of 76 Kanji (morphogram) characters which are learned in the first grade of elementary school or a set of 221 Kanji characters which are learned in the first and second grades. These easier Kanji characters were employed in order to make the comparison between Kanji and Kana meaningful. The 3 patients described are considered to be well above the level of mastering these elementary Kanji.

As for tests of Kana (syllabograms), the corresponding 76 or 221 words written in Hiragana letters were employed. This is possible because any Kanji character can be transcribed into Kana letter(s). Each Kanji character has more than two phonetic values, and consequently more than two ways of transcription into Kana letters.

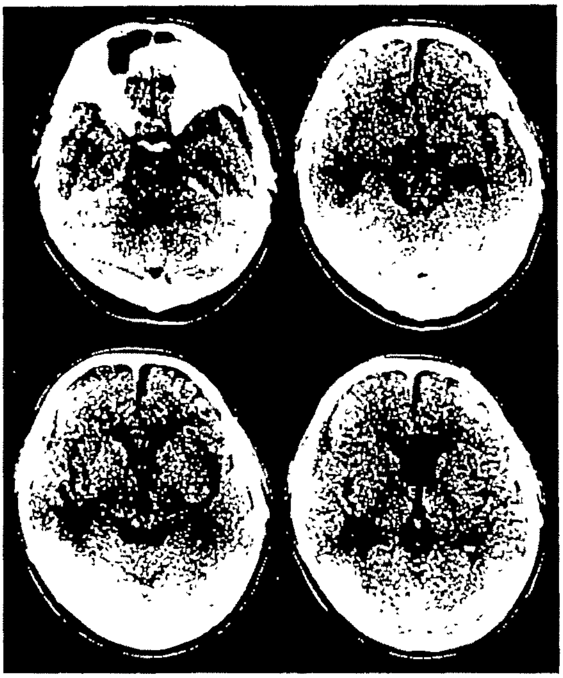

FIG. 3. CT scan from *Case 3*, 2 mos postonset showing a low density area in the left posteroinferior temporal region.

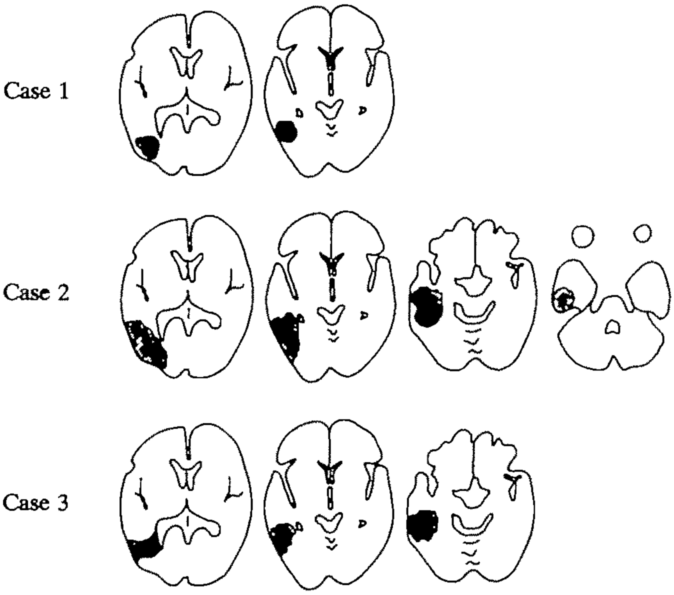

FIG. 4. Schematic diagram of CT scan findings. The left posteroinferior temporal area is damaged in all cases.

In testing the writing of Kanji characters, plural phonetic values (both On and Kun-reading) were given to the patients for a Kanji character in order to facilitate correct responses. Otherwise patients would have had considerable difficulty in choosing and writing Kanji as there are many homophones in the Kanji writing system. This is not necessary for writing Kana words to dictation since each of them has only one phonetic value.

For testing the reading of Kana we employed a phonetic sound value termed Kun-reading for a given Kanji letter. In Kun-reading the meaning of each independent Kanji is more easily and specifically determined than in On-reading, which retains the original Chinese phonetic value.

Anomia was tested by confrontation naming of either 20 common objects or 50 line drawings of common objects. The Western Aphasia Battery (WAB), Japanese edition (Kertesz *et al.*, 1982), was used as a formal examination of language disturbance.

RESULTS

Case 1

Detailed examinations of reading and writing were administered 6 and 11 mos postonset (Table 2). It is evident that alexia recovered completely by 6 mos postonset at the latest.

TABLE 2. RESULTS OF STANDARDIZED READING AND WRITING TESTS IN CASE 1*

Time postonset	*Reading aloud*		*Writing to dictation*	
(mos)	*Kanji*	*Kana*	*Kanji*	*Kana*
6	100	100	78	93
11	100	100	63	99

* Results are expressed as percentages of correct responses. The number of Kanji letters and Kana words examined was 76 for each session.

Agraphia, however, was evident, especially in Kanji. Poorer performance for Kanji than for Kana was significant both at 6 ($P < 0.01$; Student's t test) and 11 ($P < 0.001$) mos postonset. Examples of the patient's writing to dictation are shown in Table 3. When the patient failed to write a correct Kanji character, it was always because he could not recall its configuration. This means that the patient had enough knowledge concerning the meaning or pronounciation. Even when he could not recall the form of a Kanji letter, he had some knowledge of it, and could produce On-reading when Kun-reading was given by the examiner. If shown a set of multiple choices, he was always able to select the correct letter without difficulty. Paragraphia was rarely observed but was invariably noticed immediately by the patient. Copying letters was perfect. The disorder might therefore well be termed letter form amnesia. In other words, the agraphia was amnestic in nature.

The more complex the form of a Kanji character, the greater was the difficulty that the patient seemed to have in recalling it. Tests of writing which extended from 11 to 15 mos postonset demonstrated increasing difficulty in writing Kanji characters, as the grade at which they should be learned was increased; correct responses for the first, second, third and fourth grade Kanji characters were 57, 55, 36 and 29%, respectively.

TABLE 3. EXAMPLES OF WRITING TO DICTATION IN CASE 1, 11 MOS POSTONSET*

	Kanji	*Kana*	*Pronunciation*	*Meaning*
1	道 (道)	みち (みち)	[mitʃi]	road
2	(星)	ほし (ほし)	[hoʃi]	star
3	(天)	てん (てん)	[ten]	sky
4	野 (野)	の (の)	[no]	field
5	(雲)	くも (くも)	[kumo]	cloud
6	今 (今)	いま (いま)	[ima]	now
7	色 (色)	いろ (いろ)	[iro]	colour
8	艹 (草)	くさ (くさ)	[kusa]	grass
9	(強)	つよい (つよい)	[tujoi]	strong
10	妹 (妹)	いもうと (いもうと)	[imouto]	sister

* Ten Kanji letters and the corresponding Kana words (1–4 letters) were given. Correct letters are shown in parentheses. Failures were mostly in the form of no response (2, 3, 5, 9). The patient could recall only a part of a Kanji letter in 8.

This result could be interpreted either in terms of the configurational complexity or the frequency of Kanji characters, since both of them increase with the school grading.

Poor performance of writing Kana was restricted to a small number of letters (e.g., chi,ni,hi,mi,mu, ro,yu,yo,ro). This agraphia for Kana letters was also amnestic in nature.

Other neuropsychological findings 6 mos postonset were as follows. Confrontation naming of 20 common objects (subtest of WAB) was 95% correct. The rest of the WAB was well within the normal range except for the writing section; the results for the Token Test were nearly perfect (163/165 correct), apraxia or agnosia of any kind was excluded, acalculia was absent, digit span was normal, and memory deficits for recent or remote events were not observed.

Eleven months after onset, confrontation naming of line drawings of 50 common objects was 94% correct, demonstrating a very slight degree of anomia.

Case 2

Detailed examinations of reading and writing were performed 4 wks and 4 mos postonset (Table 4). Four wks postonset, alexia with agraphia was evident in which

TABLE 4. RESULTS OF STANDARDIZED READING AND WRITING EXAMINATIONS IN CASE 2*

Time postonset (mos)	*Reading aloud*		*Writing to dictation*	
	Kanji	*Kana*	*Kanji*	*Kana*
1	91	99	53	86
4	99	100	83	100

* Results are expressed as percentages of correct responses. The number of Kanji letters and Kana words examined was 221 for each session.

agraphia was more conspicuous than alexia. Discrepancy between alexia and agraphia was statistically significant for Kanji ($P < 0.001$) but was not for Kana ($P < 0.2$). The difference between the writing of Kanji and that of Kana was significant ($P < 0.001$; Student's t test). By 4 mos postonset, the alexia had recovered almost completely, leaving agraphia for Kanji as the sole feature of prominence. When the patient could not write a Kanji character, it was because she was unable to recall its form. Copying characters and letters was perfectly performed. She could choose a correct Kanji character if shown a list of multiple choices. The agraphia here was therefore also considered to be for letter form, as in Case 1.

Confrontation naming of 50 line drawings of common objects was 66% correct 4 wks postonset. Performance 4 mos postonset was 98% correct, demonstrating that anomia had improved significantly.

The rest of the neuropsychological examination was normal.

Case 3

The results of reading and writing tests 2 mos postonset were as follows. Reading aloud 76 Kanji characters and 64 Kana letters was 88% and 95% correct, respectively. Writing to dictation of 40 Kanji characters and 47 Kana letters was 38% and 98% correct, respectively. These scores could not be analysed statistically because the sets of letters examined were not matched. Reading was slow and hesitant with occasional literal (phonological) paralexia in Kana. Dissociation between reading aloud and reading comprehension was not evident. Literal (phonological) paragraphia was frequently observed in writing Kana letters. Performance in writing Kanji characters was very poor, mainly because the patient could not recall the forms of Kanji. Copying was perfect both in Kanji and Kana. This clinical picture could be summarized as alexia with agraphia of classical type associated with a left parietal lesion. Spontaneous speech was fluent and nonparaphasic, with occasional word-finding difficulties. Confrontation naming of 20 common objects (subtest of the WAB) was 85% correct. Repetition of words and sentences was perfect. Comprehension of spoken language was entirely intact. No other neuropsychological abnormalities were detected.

Follow-up study 9 mos postonset disclosed that alexia and agraphia for Kana letters had almost completely recovered, leaving amnestic agraphia for Kanji characters as the sole prominent deficit (Table 5). Confrontation naming of 50 line drawings of common objects was 96% correct, showing that the anomia had also improved significantly.

TABLE 5. RESULTS OF STANDARDIZED READING AND EXAMINATION IN CASE 3*

Time postonset	*Reading aloud*		*Writing to dictation*	
(mos)	*Kanji*	*Kana*	*Kanji*	*Kana*
9	100	98	76	100

* Results are expressed as percentages of correct responses. The number of Kanji letters and Kana words examined was 221.

DISCUSSION

Alexia with agraphia has recently been reported to occur in Japanese patients with left posteroinferior temporal lesions (Yamadori, 1982; Neshige *et al.*, 1983; Oka *et al.*, 1985; Yamadori *et al.*, 1985; Shiota *et al.*, 1986; Shimomura *et al.*, 1987). Some authors have pointed out that these lesions are associated with alexia with agraphia exclusively in Kanji (Iwata, 1984; Kawahata *et al.*, 1987; Kawamura *et al.*, 1987). To explain this phenomenon, Iwata postulated a neural pathway which connects the visual cortex with Wernicke's area, subserving semantic processing of written language. However, the detailed symptomatology of alexia with agraphia associated with left posteroinferior temporal lesions has enjoyed little agreement of opinion among authors, even less so its pathophysiological mechanism. Quite often qualitative data for the purpose of comparison of the dissociation of performance between Kanji and Kana have been lacking, and follow-up studies (Shiota *et al.*, 1986) have been rare. Therefore, even the independent status of the syndrome seemed to be in doubt.

Our detailed qualitative studies on 3 cases, however, demonstrated clearly that the persisting sign of the left posteroinferior temporal pathology is amnesia for letter form, mainly observed in Kanji, i.e., pure agraphia for Kanji. In this sense, our findings cannot be easily explained by Iwata's (1984) hypothesis, namely that this area or its subcortical neural pathways subserve semantic processing of written language. In effect, our cases were shown to be have good semantic comprehension of written language. The syndrome cannot be summarized as alexia with agraphia for Kanji either, since alexia for both Kanji and Kana, as well as agraphia for Kana, disappeared early in their course, leaving agraphia for Kanji as the sole outstanding feature in the chronic phase.

Now that we have reached the conclusion that the prominent and persisting sign of the left posteroinferior temporal pathology is 'pure agraphia for Kanji', we have to look for an explanation as to why the cases in the literature have such a wide variety of symptomatology. This problem is readily solved if we regard the symptomatology in the acute phase as a complex of symptoms which consists of alexia with agraphia of classical type, pure alexia, and pure agraphia for Kanji. The fact that the posteroinferior temporal area is located in close proximity to the angular gyrus and the occipital lobe also favours this (fig. 5). It is likely enough that a pathological process in the former area affects the latter two regions especially in its earlier phase, leading to alexia with agraphia and/or pure alexia.

It would be of considerable significance from a neurolinguistic standpoint to find an equivalent of 'pure agraphia for Kanji' in Western languages. The concept 'phonological agraphia' (Shallice, 1981; Roeltgen *et al.*, 1983) versus 'lexical agraphia' (Beauvois and Dérouesné, 1981; Croisile, 1987; Gonzalez Rothi *et al.*, 1987) sheds light on this problem. Patients with lexical agraphia are reported to have great difficulty in writing words, especially in those words whose orthography is irregular or ambiguous. Even when they failed to write a word orthographically, their writing was phonetically correct. Nonsense words were also correctly written. Kanji characters can be compared with orthographically irregular or ambiguous words, since it is impossible to write Kanji

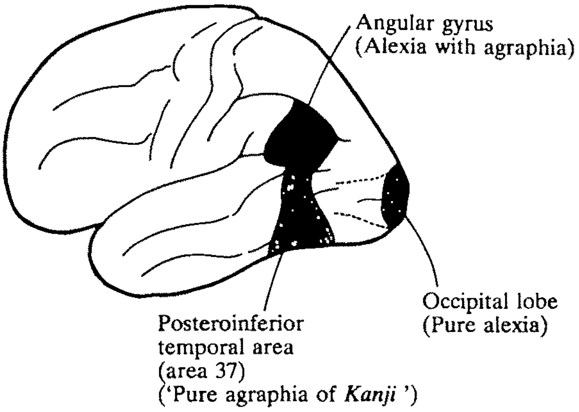

FIG. 5. Schematic representation of the lesions of alexia with agraphia, pure agraphia, and 'pure agraphia for Kanji' (lexical agraphia in the Japanese language).

characters unless each one is learned and memorized. In contrast, Kana words can be compared with orthographically regular words or nonsense words, because Kana writing always depends on strict phonological rules (almost one-to-one correspondence). The present study has demonstrated that 'lexical agraphia' does exist in the Japanese language and it takes the form of 'pure agraphia for Kanji'. Our study also agrees with that of Croisile (1987) in that lesions associated with lexical agraphia are in the left posteroinferior temporal area.

One of the most important aspects to be discussed here is the pathophysiological mechanism which underlies the syndrome of pure agraphia for Kanji. Since most of the cases in the literature, including ours, also developed anomia (amnestic aphasia), it is possible to postulate a common physiological mechanism which subserves the evocation both of words and letter forms. It was a common tendency in our patients that recall of letter forms was more difficult for Kanji characters that have more complex configurations. Another interpretation is also available in that low frequency Kanji characters present more difficulties for recall by patients, for Kanji characters of low frequency are generally more complex in their form. The latter interpretation has an advantage over the former as the frequency and familiarity of words are the most important variables for the naming disturbance in amnestic aphasia (Newcombe *et al.*, 1965; Fraisse *et al.*, 1963). Some authors (Hécaen and Albert, 1978) refer to amnestic aphasia as disorders of morpheme selection. Since Kanji characters are morphograms, amnesia for words and Kanji characters may result from a common basic disorder of morpheme/morphogram selection. The fact that anomia recovered earlier than amnestic agraphia seems to militate against our theory of a morpheme/morphogram selection disorder as a basic mechanism. The discrepancy between the two disturbances, however, could be explained by a difference in vulnerability or sensitivity between them.

The notion of pure agraphia for Kanji is also effective in explaining a paradoxical feature which sometimes accompanies pure alexia in Japanese subjects. Agraphia for morphologically complicated Kanji characters has been described in Japanese pure alexics

(Torii *et al.*, 1972; Iwata, 1977, 1986), the mechanism of which has not been satisfactorily elucidated. This phenomenon seems readily explicable in terms of the coexistence of pure alexia and the syndrome that we establish in this paper, since the lesions that give rise to both disturbances are localized continguously in the left temporo-occipital region.

It is now clear that area 37 or its subcortical white matter plays an important role in the recall of the letter forms of Kanji (fig. 5). Nonetheless, the precise anatomical substrates that are involved in this function have yet to be decided. We have the impression that the subcortical white matter plays a decisive role in it, for the lesions so far reported, including ours, were always more extensive in the subcortical white matter than in the cortex. According to Dejerine (1895) both occipital vertical and inferior longitudinal fasciculi run deep to area 37. The integrity of either one or both of these fibre tracts may be indispensable for recalling letter forms, especially those of Kanji.

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CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

CONDUCTION FAILURE BEFORE AND DURING IMMUNOGLOBULIN OR PLASMA THERAPY

by F. G. A. VAN DER MECHÉ, M. VERMEULEN *and* H. F. M. BUSCH

(*From the Department of Neurology, University Hospital Dijkzigt, Rotterdam, The Netherlands*)

SUMMARY

An earlier study has shown that patients with chronic inflammatory demyelinating polyneuropathy may improve after the infusion of fresh frozen plasma or high dose intravenous immunoglobulin. We studied 8 such responding patients with neurophysiological techniques. Before treatment all patients had decreased compound muscle action potentials (CMAP) and slowing of conduction. During several courses of treatment a progressive increase of the CMAPs occurred and in 5 patients a correlation between the CMAPs of the abductor pollicis brevis muscle and grasp force could be demonstrated. In 2 patients, increase in strength was correlated with shortening of the distal motor latency; no significant relationships were found between strength and conduction velocity.

Different patterns in the distribution of conduction failure were observed. In 2 patients, lesions were distributed along the length of the motor fibres, whereas the sensory system was spared. In another 2 patients the lesions, most likely demyelinating, were localized distally and included the sensory system. The 4 remaining patients were more difficult to classify, but individually showed greater resemblance to one or other of the two described patterns. Different patterns of conduction failure may reflect different pathogenetic mechanisms.

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is characterized clinically by symmetric weakness which progresses over a period of months or years (Dyck and Arnason, 1984). Pathophysiological changes include slowing of conduction, often not uniform over the length of the nerve, and decrease of the compound muscle action potential (CMAP) (Lewis and Sumner, 1982; Dyck and Arnason, 1984). Patients with CIDP may respond to corticosteroids (Dyck and Arnason, 1984) and to plasma exchange (Dyck *et al.*, 1986). Recently, we described the clinical effect of intravenously administered fresh frozen plasma (FFP) and polyspecific immunoglobulin (IgIV) in 17 patients (Vermeulen *et al.*, 1985); 13 patients improved, 12 considerably. In 9 patients the effect was short-lasting; they required repeated infusions to prevent relapse and to induce further improvement. Eight of these patients, seen at our centre, were studied longitudinally with neurophysiological techniques, as recently described for patients with the Guillain-Barré syndrome (GBS) (Van der Meché *et al.*, 1988). In GBS patients,

Correspondence to: Dr F. G. A. Van der Meché, Department of Neurology, University Hospital Dijkzigt, 40 Dr Molewaterplein, 3015 GD Rotterdam, The Netherlands.

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two pathophysiological patterns of conduction failure were observed in the motor fibres: in one pattern conduction failure was generalized along the length of the nerve. In the second, conduction failure was located predominantly distally in the nerves. In addition to the differences in the motor system, the sensory fibres were often spared in the first, but always affected in the second pattern.

The aims of the present study in CIDP patients were to investigate the pathophysiological changes related to clinical improvement and to compare the pattern of conduction failure with the findings in the GBS.

PATIENTS AND METHODS

Eight patients, 3 females, 5 males, median age 44, range 8–60 yrs, fulfilling the diagnostic criteria for CIDP (Dyck and Arnason, 1984) and showing improvement with FFP and in later stages with IgIV were studied. The clinical details of all but 1 patient have been described in a previous paper (Vermeulen *et al.*, 1985; Cases 1, 2, 4–8). In short, weakness without spontaneous fluctuations had been present for 2–12 months before starting treatment, and the functional deficit varied from difficulty in walking to being bedridden due to quadriplegia. Treatment consisted of 0.1 FFP/kg within 5–7 days or IgIV 0.4 g/kg daily for 5 consecutive days. All 8 patients showed considerable functional improvement.

Physiological studies were performed before and at varying intervals during treatment, depending on the rate of clinical improvement. The number of studies in the individual patients are indicated in the Results section. Median and peroneal nerves were investigated using standard EMG techniques as previously described (Van der Meché *et al.*, 1988). Care was taken to stimulate the motor fibres supramaximally. CMAPs were recorded with surface clip electrodes and the sensory nerve action potential (SNAP) of the median nerve by recording antidromically from the second finger. All potentials were recorded on paper for later measurement. Amplitudes were measured peak-to-peak. Durations of the negative phase of the CMAP after distal and more proximal stimulation were compared to detect excessive differential dispersion. This was defined as an increase in duration of the negative peak by more than 8% if stimulation was carried out at the elbow or knee rather than at the wrist or ankle, respectively (Brown and Feasby, 1984). Recording and stimulation was performed with a DISA 15-c-01 electromyograph.

RESULTS

The most important change observed during improvement of strength was the increase of the CMAPs (Table 1). The pattern of improvement of the CMAPs was, however, not identical in all patients. In the following, therefore, the pretreatment studies of the individual patients will be discussed, followed by the different patterns of improvement.

Studies before treatment

Before treatment motor conduction and CMAPs were abnormal in all patients, in studies both on the median nerve (Table 1) and the peroneal nerve. The CMAPs of the tibialis anterior (TA) and extensor digitorum brevis (EDB) muscles were most affected, being absent or below 0.25 mV in 6 of the 8 patients; this was in agreement with the predominance of clinical deficit in the legs. Early change of nerve function was, however, difficult to determine in these severely affected nerves. The CMAP of the abductor pollicis brevis muscle (ABP) present in all patients has therefore been chosen as the index for changes in motor nerve function. In all median nerves, some 'length-dependent

TABLE 1. MEDIAN MOTOR NERVE CONDUCTION STUDIES (RECORDINGS FROM ABDUCTOR POLLICIS BREVIS)

	Before treatment							*After treatment*	
Case	*APB strength (MRC)*	*DML ($<3.7\ m \cdot s^{-1}$)*	*NCV ($>51\ m \cdot s^{-1}$)*	*$CMAP_{wrist}$ (mV)*	*$CMAP_{elbow}$ (mV)*	*Excessive dispersion*	*Denervation potentials*	*$CMAP_{wrist}$ (mV)*	*$CMAP_{elbow}$ (mV)*
1	4	2.7	43	10.0	4.8	−	−	11.8	10.3
2	0	3.5	46	4.0	0.3	−	−	13.0	9.2
3	3	4.0	38	3.9	0.5	+	+	9.8	5.6
4	4	7.2	0	5.0	0.0		−	9.0	6.2
5	0	7.6	30	0.6	0.2	+	+	7.4	3.0
6	3	6.1	11	1.0	0.4	+	−	11.5	7.7
7	4	14.5	19	2.8	2.7	+	−	10.5	9.0
8	4	8.4	46	3.3	2.8	+	−	14.0	14.0

Figures in parentheses indicate the limits of normal.

CMAP reduction' was observed. This is characterized by a decrease of the CMAP after elbow stimulation compared with wrist stimulation, and can be caused by conduction block or phase cancellation between individual motor unit potentials due to excessive dispersion of the CMAP (Van der Meché *et al.*, 1988). This reduction was of significance in 4 patients (Table 1, Cases 1–4). In Cases 1 and 2, no excessive dispersion of the CMAP was present, and therefore the decrease could be confidently ascribed to conduction block (fig. 1A). This was not so in Case 3. In Case 4, the median nerve was initially not electrically excitable at the elbow despite the presence of voluntary activity in APB (MRC grade 4); conduction block could, therefore, not be determined. In the 4 patients without significant length-dependent CMAP reduction (Table 1, Cases 5–8), the CMAP was already low with wrist stimulation (≤ 2.8 mV) and decreased little with more proximal stimulation (i.e., 'simple amplitude reduction', fig. 2A; Van der Meché *et al.*, 1988). This could be due to axonal degeneration or distal demyelination. The evidently prolonged distal motor latencies (Table 1) suggest a demyelinating component. Needle EMG showed a variable extent of denervation and reinnervation

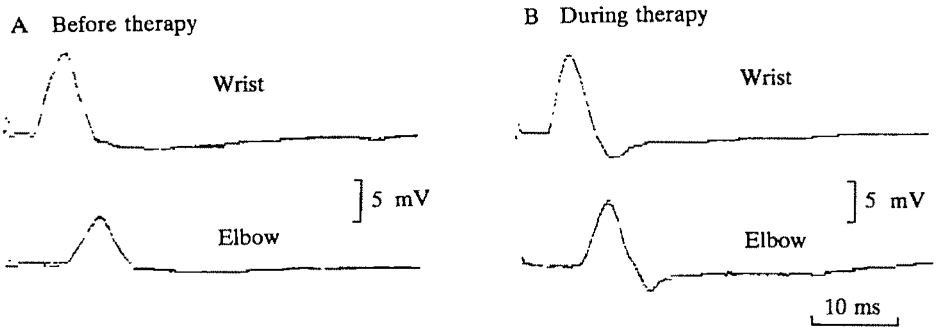

FIG. 1. CMAPs from APB in *Case 1* after stimulation of the median nerve at wrist and elbow. A, before treatment conduction block is present (i.e., length-dependent amplitude reduction without excessive dispersion). B, during treatment conduction block is reduced.

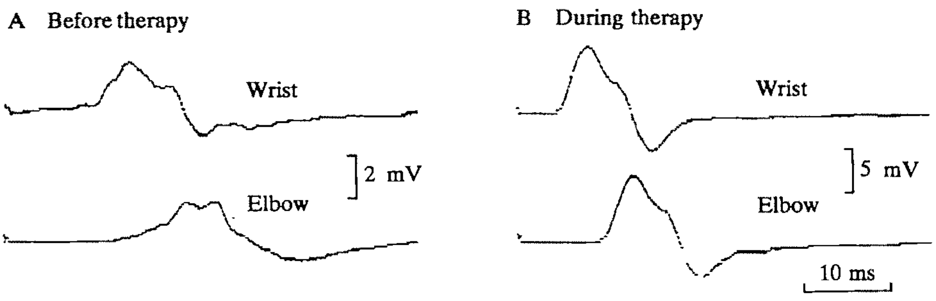

FIG. 2. CMAPs from APB in *Case 8* after stimulation of the median nerve at wrist and elbow. A, before treatment the amplitudes after wrist and elbow stimulation are both low (simple reduction of the amplitude). They are also both delayed and dispersed. B, during treatment they show similar improvement in all three aspects.

in the lower limb muscles in all patients, confirming earlier observations (Lewis and Sumner, 1982). In APB, however, signs of denervation were found only in Cases 3 and 5. The absence of denervation potentials in Cases 6–8 further suggests that distal demyelination is the most likely mechanism to explain simple amplitude reduction.

Routine clinical testing revealed sensory function to be abnormal in 6 patients and normal in 2 (Cases 1, 2). Sensory potentials were accordingly absent or present (Table 2). The 2 patients with normal sensory function and amplitudes also had normal median nerve SSEPs on both sides and their reflexes were still present with MRC grade 4 paresis.

Studies during treatment

In all patients, CMAP-APB increased during several courses of treatment (Table 1). In 5 patients, grasp force measured with a hand-held dynamometer correlated well with CMAP-APB after wrist stimulation (Table 3A). In the remaining 3 patients, the number of grasp force measurements was insufficient for correlation statistics. In 2 patients (Cases 7, 8), the distal motor latency (DML) correlated with clinical improvement (Table 3B); these decreased from 14.5 to 9.3 and from 8.4 to 3.7 ms, respectively. Significant correlations between nerve conduction velocity (NCV) and grasp force were not observed.

TABLE 2. MEDIAN NERVE SENSORY CONDUCTION

Case	*Clinical deficit**	*Reflexes present up to grade 3 strength (MRC)*	*NCV-hand* ($>60\ m \cdot s^{-1}$)	*NCV-forearm* ($>60\ m \cdot s^{-1}$)	*SNAP*$_{wrist}$ (μV)	*SNAP*$_{elbow}$ (μV)	*SSEP, wrist stimulation*
1	–	+	63	61	23	13	Normal
2	–	+	69	61	31	20	Normal
3	–	–	0	0	0	0	
4	+	–	0	0	0	0	
5	+	–	0	0	0	0	
6	+	–	0	0	0	0	
7	+	–	0	0	0	0	
8	+	–	0	0	0	0	

Figures in parentheses indicate the limits of normal. *No clinical deficit; + = decreased sensation for all modalities including two-point discrimination.

TABLE 3. CORRELATION BETWEEN GRASP FORCE AND ELECTROPHYSIOLOGICAL PARAMETERS

Case	*No. of studies*	*Regression values*	*Correlation coefficient*	*P*
A Correlation between grasp force (kPa) and CMAP-APB$_{wrist}$ (mV)				
3	8	$y = -47.3+12.7x$	0.78	<0.025
4	10	$y = 39.6+6.53x$	0.68	<0.025
6	6	$y = -3.04+4.84x$	0.98	<0.001
7	6	$y = -14.5+9.50x$	0.97	<0.005
8	11	$y = 52.5+4.30x$	0.59	<0.05
B Correlation between grasp force (kPa) and DML (ms) to APB				
7	6	$y = 14.0-0.06x$	0.91	<0.001
8	11	$y = 8.43-0.03x$	0.63	<0.025

In 2 patients, significant correlations were found between CMAP improvement of APB and TA (Cases 6, 8; r = 0.94 and 0.90, respectively). In the remaining patients, the improvement in CMAP-TA was too small and too variable to yield significant correlations.

The pattern of improvement was studied in the median nerve (fig. 3). If all conduction failure is located distally to the wrist, the recorded CMAP-APB is equal after wrist and elbow stimulation (simple amplitude reduction). During recovery, the relationship between $\text{CMAP}_{\text{wrist}}$ and $\text{CMAP}_{\text{elbow}}$ is, therefore, one-to-one (broken line, fig. 3). This is approximated by the regression lines for Cases 7 and 8 (*see* fig. 2 for original potentials). If lesions are distributed all along the nerve, the recorded CMAP-APB will decrease with more proximal stimulation (length-dependent amplitude reduction). During recovery, CMAP-APB after elbow stimulation will be consistently smaller than after wrist stimulation (fig. 1). The regression curves will, therefore, shift to the right and cut the abscissa above the zero value. This is most evident in Cases 2, 3 and 4 (fig. 3); Cases 5 and 6 take intermediate positions.

Case 1, an 8-yr-old girl, has not been included in fig. 3, since only three studies were available. She showed, however, conduction block distributed along the nerve in the pretreatment study, and a decrease of block during treatment (fig. 1, Table 1). In this patient we were able to determine the localization of conduction block more precisely with the 'inching' technique using surface-stimulating electrodes. In fig. 4 the data points are given in addition to theoretical curves; lower curve before, upper curve after treatment.

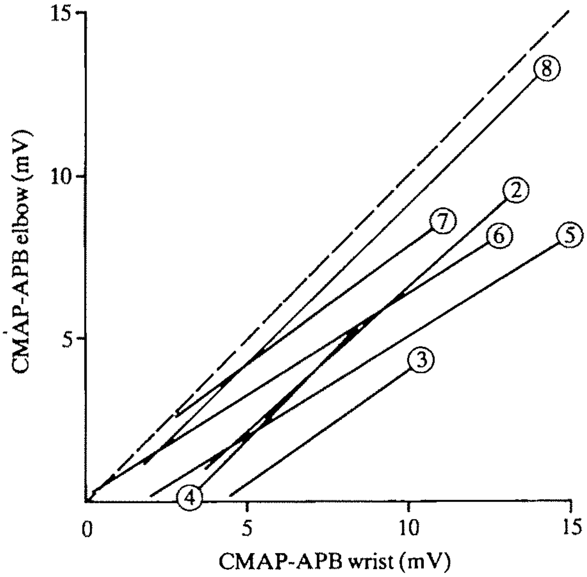

FIG. 3. Regression lines of individual patients describing the relationship between CMAP-APB after wrist and elbow stimulation during clinical improvement. All relationships were statistically significant (Table 4). Numbers correspond to patient numbers used in all tables and text.

TABLE 4. CORRELATION BETWEEN CMAP-APB$_{\text{wrist}}$ AND CMAP-APB$_{\text{elbow}}$ (mV)

Case	*No. of studies*	*Regression values*	*Correlation coefficient*	*P*
2	7	$y = -2.30+0.89x$	0.95	<0.001
3	8	$y = -2.81+0.68x$	0.74	<0.025
4	10	$y = -2.94+0.96x$	0.69	<0.025
5	10	$y = -1.10+0.62x$	0.95	<0.005
6	6	$y = 0.05+0.63x$	0.94	<0.005
7	6	$y = 0.64+0.72x$	0.96	<0.005
8	11	$y = -0.46+0.96x$	0.97	<0.005

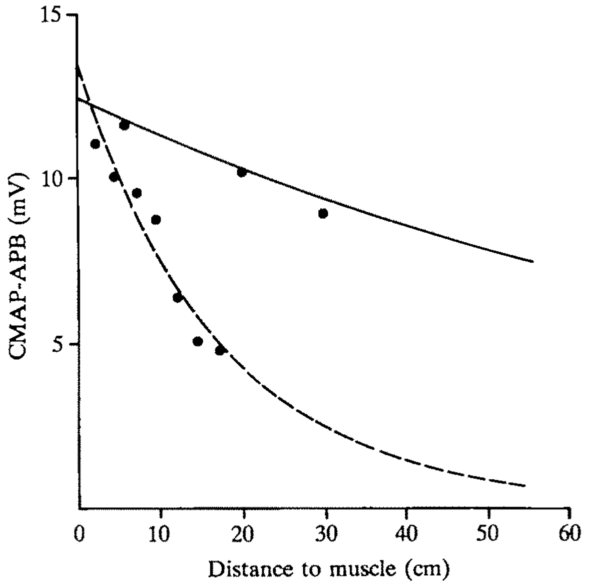

FIG. 4. Relationship between CMAP-APB and distance between stimulus electrode and muscle in *Case 1*; lower curve before, upper curve after treatment. Filled circles represent the actual EMG measurements. The curves have been calculated assuming a random distribution of conduction block (Van der Meché *et al.*, 1985; Van der Meché and Meulstee, 1988).

These curves are calculated, assuming that the lesions are randomly distributed (Van der Meché *et al.*, 1985; Van der Meché and Meulstee, 1988). This figure suggests that the experimental findings are compatible with a random distribution of lesions.

DISCUSSION

The pretreatment studies of these 8 CIDP patients confirm the earlier findings described by others (Lewis and Sumner, 1982; Dyck and Arnason, 1984), namely nonuniformity of slowing of conduction and decrease of the CMAPs. During several courses of FFP or IgIV therapy the CMAPs invariably increased (Table 1). In 5 patients with measurable grasp force at the onset of therapy this clinical parameter correlated well with CMAP-APB after wrist stimulation. In contrast, a significant relationship between the DML to APB and the grasp force was only found in 2 patients, and between the NCV and grasp force in none. This confirms earlier observations that latencies or conduction velocities can improve during clinical improvement but not obligatorily (Prineas and McLeod, 1976; Dalakas and Engel, 1981). In contrast, CMAPs always increased indicating an increase of the number of conducting motor axons irrespective of their velocity.

Although CMAPs were below normal in amplitude in all patients, further analysis showed different patterns of conduction failure. In the pretreatment studies conduction block was found along the length of the motor fibres in Cases 1 and 2. Conduction block is defined as a length-dependent amplitude reduction in the absence of excessive dispersion and is related to widespread demyelination (Feasby *et al.*, 1985). The sensory fibres in the same mixed nerve segment, however, were spared. Clinically, no sensory deficit was evident, not even in Case 2 when he was quadriplegic. Cases 7 and 8, in contrast, showed a simple amplitude reduction, i.e., low and similar CMAPs after wrist and elbow stimulation. This can be explained by axonal degeneration or distal demyelination. Since no denervation potentials were observed in APB of these 2 patients and the DMLs were very prolonged, distal demyelination is the more likely mechanism. This conclusion is further supported by the observations that clinical improvement was similar as compared with Cases 1 and 2 and during improvement the DMLs showed a significant decrease in relation to the increasing grasp force. Cases 3–6 were less easy to categorize, although Cases 3 and 4 showed greater resemblance to the former pattern and Cases 5 and 6 to the latter.

These patterns of conduction failure were further confirmed during improvement. Cases 1 and 2 showed a progressive decrease of conduction block in addition to some increase of the distal CMAP, whereas Cases 7 and 8 showed predominantly an increase of the distal CMAP (figs 1–3).

The widespread distribution of conduction failure in Cases 1 and 2 is comparable with findings in a subgroup of Guillain-Barré patients (Van der Meché *et al.*, 1988; group A). It has been suggested that the distribution of lesions might well be random (Van der Meché and Meulstee, 1988). This could also be true for Case 1 of this study (fig. 4). The distal localization of conduction failure in Cases 7 and 8 is reminiscent of the group with distal lesions in motor and sensory nerves in the Guillain-Barré study and we suggested that distal demyelination is one of the mechanisms for a low distal CMAP. Recently, it has been shown that in the GBS a low distal CMAP predisposes to a more severe course (Cornblath *et al.*, 1988) and the authors suggested that low distal CMAPs in general are caused by axonal degeneration. This conclusion is, however, not in accordance with our more detailed observations in both GBS and CIDP patients. Some patients have low CMAPs without denervation potentials in needle EMG studies and may improve rapidly, which is compatible with remyelination. Therefore, low CMAPs should not lead to therapeutic nihilism.

Cases 3–6 were more difficult to classify as compared with the patients in the Guillain-Barré study. This might be explained by a more prolonged disease process: in the later phase of the GBS it was also observed that the original pattern could be obscured. On the other hand, the distinct patterns as seen in some of the patients could intermingle in other patients and give rise to intermediate patterns.

In conclusion, 8 responding patients were followed during treatment with FFP or

IgIV. During several courses of treatment the CMAPs increased as evidence of an increase in the number of conducting axons; in 5 patients a correlation between increase in CMAP and increase in strength could be demonstrated. The distribution of pathophysiological lesions was, however, different in individual patients; this may reflect different pathogenetic mechanisms.

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ABNORMALITIES OF NONVISUALLY-GUIDED EYE MOVEMENTS IN PARKINSON'S DISEASE

by TREVOR J. CRAWFORD,[1] LESLIE HENDERSON[1,2] *and* CHRISTOPHER KENNARD[1]

(From the [1]*Department of Neurology, The London Hospital, London, and* [2]*Department of Psychology, Hatfield Polytechnic, Hatfield, Herts, UK)*

SUMMARY

Rapid eye movements (saccades) were examined in 7 patients with idiopathic Parkinson's disease (PD) and a matched group of normal control subjects. The effect of instructional and stimulus conditions used to elicit saccades was examined using 3 experimental paradigms. Eye movements directly elicited by a novel peripheral target were unimpaired in patients with PD as compared with control subjects. Saccades to a remembered target location, however, were dysmetric in the PD group and showed a characteristic multistepping pattern. The PD impairment was not caused by a loss of information on target location since their final eye position was close to the target at all eccentricities. Peak velocity, duration, and latency did not distinguish between PD patients and controls. These results support the view that for saccades which are not directly elicited by a visual target there is a neural pathway that can be distinguished from structures involved in the generation of visually elicited (or 'reflexive') saccades. The finding that in PD saccades to a remembered target are selectively impaired suggests that structures in the basal ganglia play a crucial role in this alternative pathway.

INTRODUCTION

In recent years there has been converging evidence regarding the role of the basal ganglia in motor behaviour. It has been shown from a number of perspectives that pathology of the basal ganglia leads to impairment in the control of movements, particularly in tasks with reduced visual or environmental information for eliciting or guiding movement.

It is known that the basal ganglia not only process visual information (e.g., Caan *et al.*, 1984) but many cells in the caudate nucleus and globus pallidus are selective for movements that are executed in response to a visual stimulus (Aldridge *et al.*, 1980). In recent animal neuropharmacological studies, Hikosaka and Wurtz (1985*a, b*) and Gelissen and Cools (1987) found that the substantia nigra, pars reticulata to superior colliculus pathway plays a crucial role in the generation of nonvisually-guided movements. In clinical studies of patients with Parkinson's disease (PD) it has been shown that temporary deprivation of sight of the target during a manual tracking task severely compromises their performance. Once the target is restored performance improves substantially (Flowers, 1978; Cooke and Brown, 1979; Stern *et al.*, 1983). These studies

Correspondence to: Dr C. Kennard, Department of Neurology, The London Hospital, London E1 1BB, UK.

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suggest that the extent to which a movement is visually guided (or utilizes external references) is one important dimension in the general organization of movement. However, there is no adequate model of the neural pathways involved in the control of different categories of limb movements. Recent eye movement research has begun to address this issue.

There are a number of different ways in which rapid eye movements (saccades) can be used to foveate a target. Human saccadic eye movements have therefore been studied with a number of different target paradigms in an attempt to elucidate the contribution of specific neural centres to the generation of different types of saccades. In the most commonly used saccadic paradigm, a saccade is triggered 'reflexively' to the onset of a peripheral target. Other paradigms require a more 'volitional' element in the saccade generation. For example, in the 'antisaccade' target paradigm saccades are required which are of the same amplitude but in a direction opposite to the target. In the 'remembered' target paradigm a saccade is summoned to the location where a target had previously been briefly present.

It is becoming evident from studies which have used these target paradigms that the extent to which cortical and midbrain oculomotor centres contribute to the control of saccadic eye movements depends crucially on the stimulus configuration and task specification used to elicit eye movements. Frontal lesions produce impairments of antitarget and remembered target saccades, while reflexive saccades are unimpaired (Guitton *et al.*, 1985; Deng *et al.*, 1986). In Huntington's disease, a disorder affecting the basal ganglia, there is an impairment both of remembered saccades and the ability to inhibit saccades in the presence of a distraction target (Leigh *et al.*, 1983; Lasker *et al.*, 1987).

In the other major clinical disorder of the basal ganglia, Parkinson's disease, a number of studies have reported an impairment in saccadic eye movements (DeJong and Melvill Jones, 1971; Melvill Jones and DeJong, 1971; Corin *et al.*, 1972; Shibasaki *et al.*, 1979; Teräväinen and Calne, 1980. White *et al.*, 1983), but there are disagreements on the extent of the dysfunction. In mildly affected patients (Gibson *et al.*, 1987) there is remarkably little evidence of any impairment in reflexive saccades. However, in certain other paradigms eye movement abnormalities may be more clearly identified. For example, Bronstein and Kennard (1985) found that patients with PD, when compared with normal subjects, are less able to anticipate a regular target step and make a predictive saccade. It may be that this particular difficulty is a manifestation of a more general impairment in generating nonvisually-driven saccadic eye movements. A recent study has shown that under some circumstances patients with PD can in fact produce anticipatory saccades; however, such saccades are considerably more hypometric than those of control subjects (Crawford *et al.*, 1989). Moreover, Carl and Wurtz (1985) have presented a brief abstract reporting that in 3 hemiparkinsonian subjects saccadic velocities for remembered saccades were diminished, but only when directed contralateral to the impaired side.

In the present investigation we compared reflexive saccades with saccades to remembered target locations in mild to moderately affected patients. We reasoned that if the basal ganglia are particularly important in the processing of nonreflexive saccades in the absence of visual feedback, then parkinsonians should show abnormalities in the generation of saccades of this type. We therefore conducted a study of saccadic eye movements in PD under a number of visual target conditions. The nonvisually-guided task was similar to the remembered (REM) target task used in animal studies (Hikosaka and Wurtz, 1985*a*, *b*), while the visually-guided task used the standard procedure for eliciting reflexive saccades to random target steps. There was a possibility that any parkinsonian saccadic impairment in the REM task was due to an incidental property of the sitmulus configuration in the REM task. In this task the peripheral target is exposed while the subject is still fixating a central target. Previous studies have shown that when 2 targets are displayed concurrently in a visual hemifield, a saccade is directed to an intermediate position between the 2 targets (i.e., towards the apparent 'centre of gravity'; *see* Findlay, 1982, and Findlay and Crawford, 1983). Although the 'centre of gravity' effect is usually demonstrated when both targets are presented to one side of the vertical meridian, it is possible that this mechanism could be operating in the REM task. We therefore included a control paradigm to examine this possibility by using a temporal target overlap (OLP) condition.

MATERIAL AND METHODS

Subjects

Seven PD patients (4 females, 3 males), mean age 61 (range 52−71) yrs, agreed to take part in this study. The control group consisted of 7 age-matched subjects (4 females, 3 males; mean age 63, range 53−72 yrs), none of whom had known neurological or visual impairment. No control subject was taking psychotropic medication. The parkinsonians were assessed on the Webster (1968), Hoehn and Yahr (1967) and the minimental state dementia scale. The clinical ratings of the PD patients are shown in Table 1. None of our patients showed signs of dementia and they were all receiving their normal medication (L-DOPA or bromocriptine) at the time of testing.

Eye movement recording and target paradigms

Eye movements were recorded by an infrared scleral reflection device (ACS EM130). The frequency range was flat to 80 Hz and the system was linear over ± 15° with a resolution of 15 min arc. Eye position was differentiated electronically (3 dB point, 60 Hz) to obtain eye velocity. Peak velocity was therefore measured at the point of maximum analogue output during the saccade. The stimulus and eye movement data were recorded on a Mingograf chart recorder, which had a frequency response greater than 200 Hz,

TABLE 1. PATIENT DETAILS AND PARKINSONIAN MOTOR ASSESSMENT

PD patients	*Age/Sex (yrs)*	*Webster/Hoehn Yahr*
1	58 F	5/I
2	62 F	3/I
3	71 F	1/I
4	68 F	6/III
5	54 M	4/I
6	52 M	5/II
7	62 M	5/II

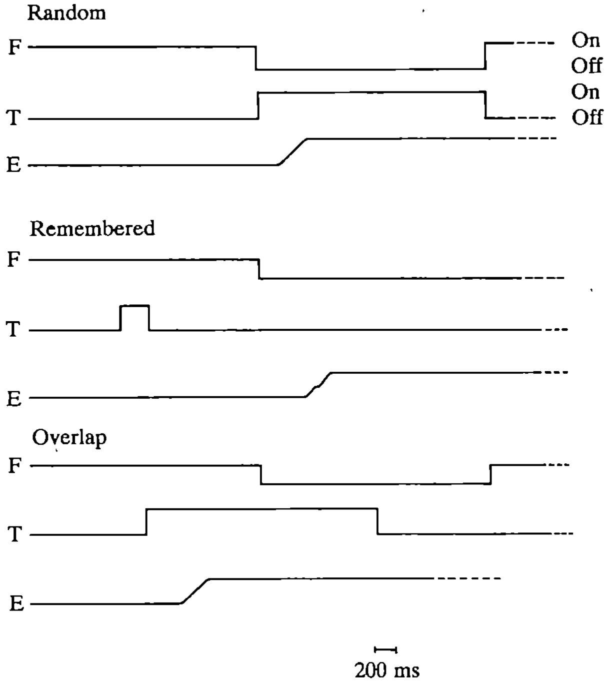

FIG. 1. Diagram of the random, remembered and overlap experimental paradigms, showing the fixation (F) stimulus, peripheral target (T) and an illustrative eye movement (E).

and on analogue tape. Subjects were seated 150 cm from the target array. Nine green LED targets, each of which subtended 0.25°, were located at 3.75° intervals from the centre position out to +15° and −15° in the periphery. The target paradigms were controlled by an Apple II+ microcomputer. Targets were presented in a randomized and counterbalanced design such that each of the 8 targets was presented 6 times. The experiments were conducted in the dark. Head movements were restrained by a head support with an adjustable head band. Each subject was tested in three conditions: reflexive random (RAN), remembered target (REM), and temporal overlap (OLP) conditions. These trial formats are shown in fig. 1.

In the visually-guided RAN condition a trial commenced with the onset of the centre LED. After a period of 1 s this LED was turned off and replaced by 1 of the 8 peripheral target LEDs selected at random; 1 s later the target LED was turned off and the centre LED reappeared. The subjects were asked to move their eyes quickly and accurately to whichever peripheral LED came on.

The second visually-guided condition, OLP, was very similar to that of RAN (*see* fig. 1) with the addition that a temporal centre-peripheral target overlap was introduced. A trial commenced with the onset of a centre fixation LED as in the RAN condition. After 1 s, 1 of the 8 peripheral LEDs was illuminated for a period of 1 s. At the same time the central fixation LED remained on for a further 500 ms; 2 LEDs were thus visible for this period. As in the RAN condition, subjects were asked to move their eyes quickly and accurately to the peripheral target as soon as it appeared.

In the middle section of fig. 1 the sequence of events in the REM condition is shown. The total duration of the centre LED from trial onset was 1500 ms, and after 800 ms a peripheral target was presented for 200 ms. Subjects were instructed to maintain fixation at the centre and not to move their eyes towards the peripheral LED until the centre LED went off 500 ms later. The offset of the centre LED, which occurred simultaneously with a 200 ms tone from a centrally presented tone generator, was the cue to make a saccade to the location where the target had appeared. Subjects received a block of practice trials to ensure that they fully understood the object of the test; 48 trials of each paradigm were presented.

Primary saccade data were digitized from the chart records by hand using a digitizing tablet on a Tektronix 4052 processor with a spatial resolution of 0.01 inch. Measurements of amplitude, peak velocity, duration, latency and accuracy were extracted from the data. The identification and rejection of movement artefacts introduced by blinks and head movement was achieved by visual inspection of each saccade.

Two measures of the accuracy of the primary saccade were calculated from the saccade gain (saccade amplitude/target amplitude) of each saccade. The mean gain provided a measure of constant error; that is, the overall tendency towards undershoot or overshoot of the target. A gain of unity therefore denotes perfect accuracy; gains below and above unity represent undershoot and overshoot, respectively. The SD of a subjects's gain values within a condition expressed variable error: that is, the randomly varying component in the subject's responses. Statistical analyses were performed using ANOVA and Student's t test.

RESULTS

Fig. 2 shows the distribution of saccade latencies in the REM task. It is evident that the proportion of saccades preceding the movement cue for a saccade (i.e., the offset of the fixation target) is no different for PD patients and controls. In both groups on approximately 30% of the trials, saccades occurred before the movement cue. These early saccades were analysed separately in the subsequent analyses.

There was a significant effect of the type of task on saccade latencies (F(2,24) = 12.46, $P < 0.01$). The group factor (PD vs Controls) was not significant, nor was there a significant group by task interaction, showing that the subject group factor was not differentially affected by the target condition. PD patients (t = 2.42, $P < 0.05$) and controls (t = 2.85, $P < 0.05$) produced longer saccade latencies in the REM task (fig. 3). Although PDs appear to have a faster mean reaction time in the REM task compared with the controls, this was not statistically significant (P(t) = 0.28).

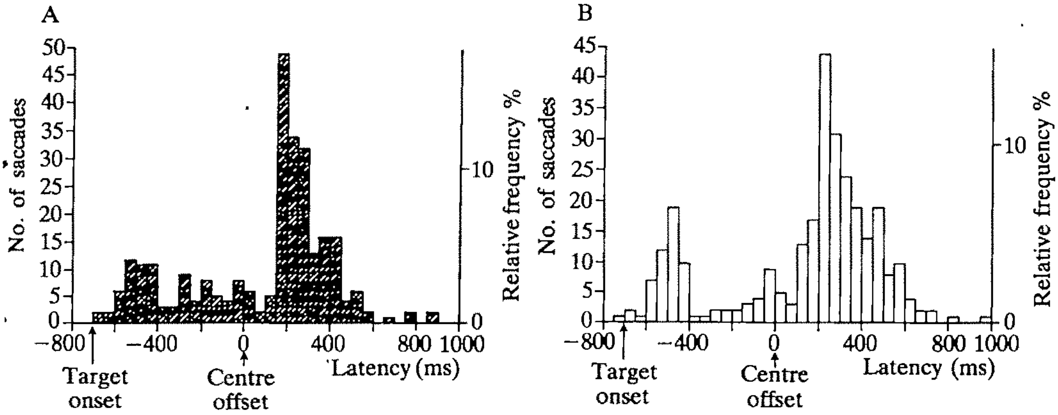

FIG. 2. Histograms showing the distribution of saccadic latencies in the remembered (REM) target paradigm. A, PD patients; B, controls.

TABLE 2. MEAN SACCADIC GAIN (SACCADE AMPLITIDE/TARGET AMPLITUDE)

PD patients	*RAN**	*OLP**	*REM**	*Early REM**
1	1.15	1.16	1.19	0.88
2	0.94	0.92	0.67	0.79
3	0.97	0.98	0.75	0.90
4	0.89	0.95	0.82	0.63
5	0.98	0.98	0.77	0.58
6	0.92	0.93	0.90	0.72
7	1.14	1.03	0.90	1.22
Mean	1.0	0.99	0.85	0.81
Controls				
1	0.92	0.96	0.91	0.87
2	0.99	0.89	0.86	0.81
3	0.83	0.86	0.98	–
4	1.03	0.89	0.85	1.05
5	0.84	0.81	0.98	0.97
6	0.92	0.92	0.88	0.83
7	1.10	1.14	0.89	1.07
Mean	0.95	0.92	0.91	0.93

* For explanation of abbreviations, *see* text.

The mean gains were entered into a two-way ANOVA with groups (PD vs Controls) and target conditions (REM, OLP and REM) as factors. The main effect of conditions was significant ($F(2,24) = 5.45, P < 0.05$). Neither the group factor nor its interaction with conditions was significant. These data are displayed in Table 2, from which it can be seen that the effect of conditions takes the form of hypometric responses to the target in the REM condition. The overall difference between the RAN and REM conditions is reliable ($t = 2.44, P < 0.05$). Although the PD patients showed a tendency to greater undershoot in the REM condition, this did not reach significance.

Table 2 also shows in the REM condition the mean gain for saccades that preceded the movement cue (*see* fig. 2). These values show that our elimination of trials where there is a failure to inhibit early saccades is conservative. Interestingly enough, these early saccades are as hypometric overall as those that follow the cue and the tendency towards greater hypometria in the PD group is more marked.

The variable error component was also subjected to a two-way ANOVA. The effect of conditions was again significant ($F(2,24) = 11.41, P < 0.01$). While there was no overall effect of groups a significant interaction between group and conditions ($F(2,24) = 4.87, P < 0.05$) indicated that the inaccuracy evident in the REM condition was greater in the PD group. Whereas the difference between groups was not significant in the RAN condition, it was reliable in the REM condition ($t = 1.86, P < 0.05$). This selective effect of the REM task on the PD patients is shown in fig. 4. As with saccade gain, a separate analysis of the early saccades in the REM condition revealed the same pattern, with variable error greater in the PD early saccades (mean 0.33) than in the controls (mean 0.23).

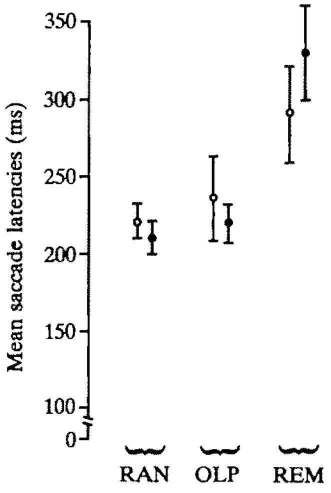

FIG. 3. Mean saccade latencies and SEMs in random (RAN), overlap (OLP) and remembered (REM) target paradigms. Saccade latencies are increased for PD patients and controls in the REM condition. Open circles = PD patients; closed circles = controls.

Examination of the two error coefficients for the OLP condition shows clearly that we can reject the hypothesis that inaccuracy in the REM condition is simply due to the simultaneous presence of the 2 stimuli when the target location is specified. For neither type of error does the RAN condition differ significantly from the OLP.

The mean gains are shown for the two groups at each target eccentricity in Table 3. The tendency for PD patients to exhibit a greater impairment in saccade accuracy is not systematically qualified by target amplitude. It is particularly notable that the tendency towards a greater REM deficit is not confined to the larger target amplitudes.

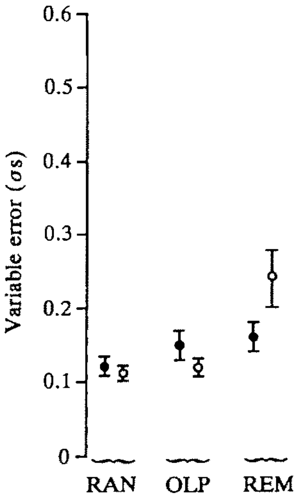

FIG. 4. Mean variable error (SD of gain) for both groups in the random (RAN), overlap (OLP) and remembered (REM) target paradigms. PD saccade accuracy deteriorates in the REM paradigm. Open circles = PD patients; closed circles = controls.

TABLE 3. MEAN SACCADIC GAIN AT EACH TARGET AMPLITUDE

Target amplitude (deg)	3.75	7.5	11.25	15.0
PD patients				
RAN*	1.07	0.99	0.97	0.88
REM	0.93	0.79	0.89	0.84
Controls				
RAN	1.06	0.90	0.91	0.90
REM	0.95	0.86	0.95	0.88

* For explanation of abbreviations, *see* text.

Fig. 5 illustrates examples of parkinsonian saccades in the REM task. These examples show that inaccurate primary saccades frequently take the form of a markedly undershooting saccade followed by a sequence of multistepping saccades continuing in the same direction. One feature of note is the short latency of these secondary saccades. Intersaccadic intervals of less than 100 ms were found in 48% of the secondary saccades of this patient. Brief intersaccadic intervals have also been reported by Teräväinen and Calne (1980), who observed intervals as short as 20 ms. The short intersaccadic intervals of our patients were in the range of 50 to 100 ms.

A response on a given trial was classed as a multiple saccade if there were at least 3 components, or 2 components with the primary saccade less than half the amplitude

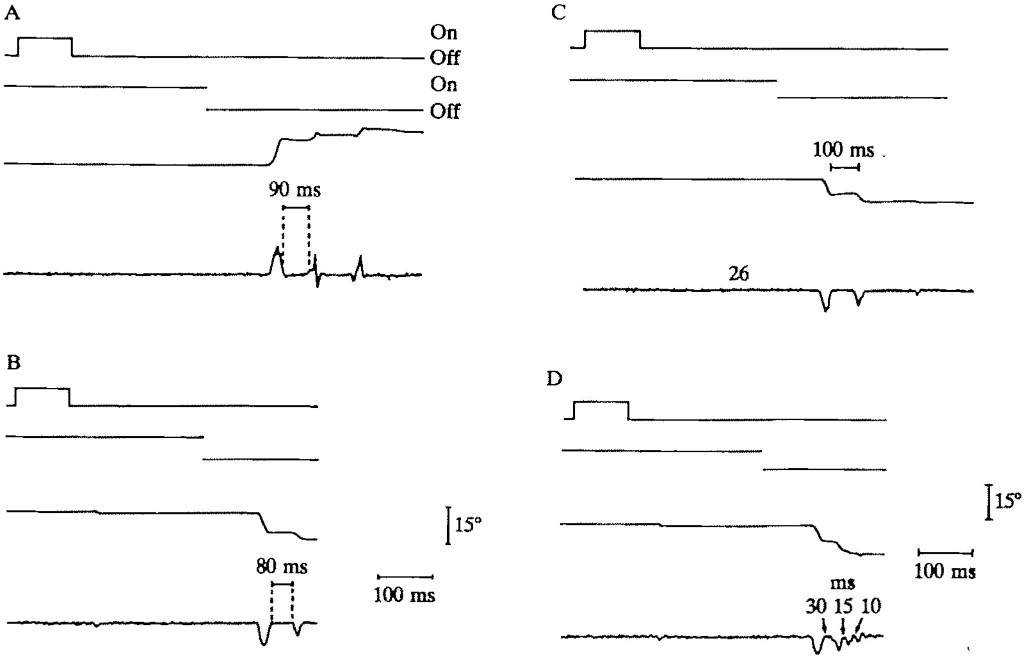

FIG. 5. Examples of PD multistepping and short intersaccadic intervals in the REM paradigm. A and B show the target flash and the relative timing of centre LED offset. C and D show eye position and eye velocity.

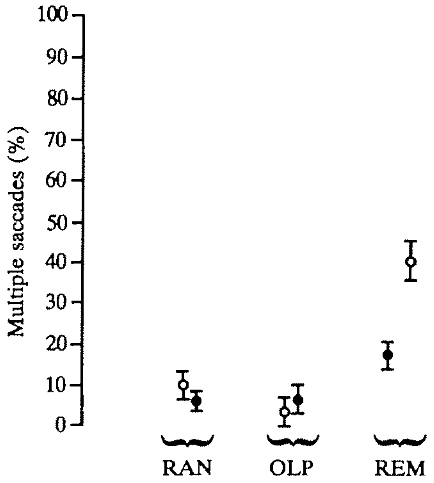

FIG. 6. Mean proportion of multiple saccades in the random (RAN), overlap (OLP) and remembered (REM) target paradigms. Both groups show increased multiple saccades in the REM condition. However, this increase is greater for the PD patients than the control subjects. Open circles = PD patients; closed circles = controls.

of the final eye position. An ANOVA revealed a main effect of group with PD patients showing many more multiple saccades (F(2,24) = 9.852, $P < 0.01$). There was a significant main effect of task (F(2,24) = 31.874, $P < 0.01$), principally due to the increased incidence of multiple saccades in the REM condition. Furthermore, there was a reliable group by task interaction (F(2,24) = 8.4089, $P < 0.01$), which appeared to be due to the larger effect of the REM condition on the PD patients. The pairwise t test analyses of the incidence of multiple saccades showed that the PD patients produced far more of such saccades in the REM condition ($P < 0.001$). Although controls also generated more multiple saccades in this condition ($P < 0.05$), the effect was significantly larger in the PD patients ($P < 0.01$; *see* fig. 6).

In many cases these multiple saccades succeeded in carrying the eye close to the target position. Thus despite the hypometria of the primary saccade, the secondary saccades enable the eye to reach the correct target position. Fig. 7 shows the mean final eye positions in relation to the target eccentricities. In the REM condition there was no reliable difference between the PD and control groups in final eye position. The mean final eye positions of both PD patients and controls lay slightly beyond the target, with the exception of the controls at 15°, where the mean was 14.6°. The parkinsonian selective abnormality with REM targets is therefore not due to a selective loss of spatial information about the target position.

Since it is well known that saccadic velocity is an increasing function of amplitude a best-fit curve of the form $Y = A+B\times\log(X)$, where A and B are coefficients (the intercept and slope) and X and Y represent amplitude and velocity, respectively, was calculated individually for each subject for both the RAN and REM conditions. Saccadic velocities at 3 amplitudes were then extracted from these curves (5°, 10° and 15°) and the velocities subjected to a three-way ANOVA (Group×Task×Amplitude). These data are shown in Table 4. There was a significant effect of saccade amplitude (F(2,24) = 331.3, $P = 0.01$), confirming that saccade velocity increased with amplitude. There

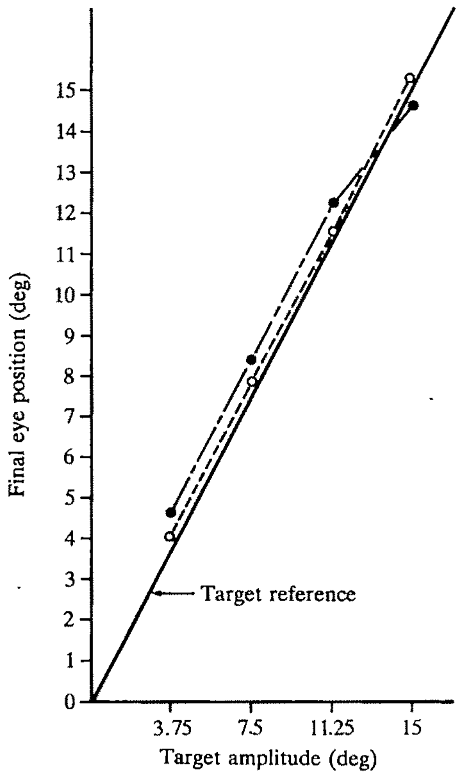

FIG. 7. Final eye positions of controls in the REM target paradigm. Open circles = PD patients; closed circles = controls.

was also a significant effect of task (F = 4.72, $P < 0.05$) on saccade velocities but no interaction with saccade amplitude or subject group. This effect of the saccade task and the absence of an interaction with the group factor showed that the lower velocities in the REM task applied both to PD patients and the controls.

DISCUSSION

The results of this study show that patients with PD have a specific impairment in the generation of saccades to remembered targets. The parameters which most clearly revealed this deficit were the accuracy of the primary saccade and the incidence of multiple

TABLE 4. MEAN VELOCITIES (DEG/s) AND SDs (IN BRACKETS) IN REM AND RAN TASKS

	*RAN**			*REM**		
Saccade amplitude (deg)	5	10	15	5	10	15
PD patients	235 (21)	330 (29)	385 (36)	225 (46)	312 (76)	364 (95)
Controls	246 (35)	340 (31)	395 (30)	204 (36)	291 (53)	342 (67)

* For explanation of abbreviations, *see* text.

saccades. Interestingly, in other saccadic tasks which show a parkinsonian deficit, dysmetria is also a major feature (DeJong and Melvill Jones, 1971; Teräväinen and Calne, 1980). Patients with Huntington's disease also similarly generate inaccurate saccades to remembered targets (Lasker *et al.*, 1987). Moreover, the nature of this deficit is comparable to that found in ballistic limb aiming movements in both human (Flowers, 1978; Hallett and Khoshbin, 1980) and animal (Caan and Stein, 1979) studies.

One possible interpretation of this parkinsonian selective deficit in the REM condition is that the increased inaccuracy stems from a decay of spatial information (i.e., defective memory) about the target location; this would yield a false estimation of target amplitude. We believe that this hypothesis can be rejected on the grounds that the corrective saccades in PD following the initial saccadic error resulted in the final eye position approximating to that of the target position and do not differ from the final eye position of the controls.

Another account of the deficit found in the REM condition which can be rejected is that the hypometric primary saccade is due to the simultaneous appearance of a target and fixation stimulus (e.g., the 'centre of gravity' effect). This characteristic is shared by the OLP task in which no deficit was found in either group.

In the present study the REM paradigm produced effects on both saccadic velocity and latency, which showed no consistent difference between PD patients and controls. Our findings that normal subjects, as well as PD patients, show overall reduced velocities in REM saccades, is consistent with recent results (Smit *et al.*, 1987) using a similar paradigm in normal subjects. Whether time-based measures such as latency and peak velocity are found to be abnormal in PD may depend on other factors such as patient selection and experimental conditions.

The suggestion that the impaired accuracy of parkinsonian saccades to a remembered target is a selective deficit requires the following qualifications. First, the finding that conventional RAN saccades are of normal accuracy in PD may hold only for relatively mildly impaired or stably medicated patients. In advanced disease where the underlying pathology is less circumscribed, it may be more difficult to detect selective deficits. Secondly, the reliance of PD patients on a target that directly elicits the saccade is not confined to random steps since we have also shown impaired accuracy for predictive saccades in PD (Crawford *et al.*, 1989; *see also* DeJong and Melvill Jones, 1971; White *et al.*, 1983).

We now turn to consider, in a wider context, the source of this selective difficulty. Two factors may be relevant to the interpretation of this deficit. First, in a wide range of tasks PD patients perform better when visual feedback can be used to control their motor output (*see* Flowers, 1978; Cooke and Brown, 1979; Stern *et al.*, 1983). A simple example of this phenomenon was highlighted by Hore *et al.* (1977), commenting on Martin's (1967) clinical observations: 'In one test for motor defects, patients were asked to reach out with their arm at shoulder height and touch alternately the tips of the examiner's two forefingers which were held about a foot apart. With their eyes open the patients continued to perform well for several minutes . . . but if after the first movements he closes his eyes, the hand almost immediately falls away and the movement peters out.' It is likely, therefore, that absence of on-line visual information may be of particular significance in the REM deficit. Secondly, an alternative interpretation relates to the possibility that parkinsonian difficulties may be magnified when saccades have to be internally or voluntarily (as opposed to reflexively) elicited. Highstein *et al.* (1969) found that patients produced more multistepping saccades when voluntary saccades triggered on verbal command, were compared to visually-directed saccades (*see also* Melvill Jones and DeJong, 1971). The extent to which the deficit will be manifested may, therefore, depend critically on whether external stimuli are available to elicit the response or whether the response is internally generated.

In an attempt to provide a schematic neural model of saccadic systems, Zee (1984) has drawn attention to two types of saccades and their supranuclear neural correlates. What may be called type A saccades are those quasireflexive saccades which are generated to the onset of a 'new' target in the peripheral environment. Type B saccades can be described as voluntary saccades elicited to internal cues or symbolic external target cues. Type A saccades are thought to be largely the prerogative of superior colliculus function, while the frontal eye fields feature in the control of type B saccades. Consistent with this scheme was the finding that although frontal lesions lead to abnormalities in directing antisaccades in man (Guitton *et al.*, 1985) and REM saccades in monkeys (Deng *et al.*, 1986) reflexive saccades are relatively unimpaired. Recent neurophysiological studies in the monkey by Hikosaka and Wurtz (1983) have demonstrated that some neurons in the substantia nigra, pars reticulata and caudate nucleus (Hikosaka and Sakamoto, 1986) alter their firing rate in response to saccades to remembered targets, but not to reflexive saccades. Furthermore, neuropharmacological inhibition of substantia nigra, pars reticulata-collicular pathways led to a reduction in saccadic velocities and amplitudes specifically to remembered targets (Hikosaka and Wurtz, 1985*a*, *b*).

The pathology of PD primarily involves a degeneration of the dopaminergic neurons in the substantia nigra, pars compacta. There are two projections of these neurons which might account for abnormalities in saccadic eye movements. The major projection is to the striatum, and dopamine deficiency at this site may lead to an abnormality of the inhibitory outflow, via the substantia nigra, pars reticulata, occurring prior to a remembered saccade. This would result in impaired disinhibition of the superior colliculus. Alternatively, a pathway from the substantia nigra, pars compacta to the superior colliculus, presumed to be dopaminergic, has recently been described in man (Johnson *et al.*, 1987). As there are no data concerning the activity of this pathway in animals in relation to saccades it can only be surmised that its degeneration and the resulting lack of dopamine in the superior colliculus would result in abnormal saccades.

It is interesting to compare the saccadic deficit in another disease, Huntington's disease, in which there is a degeneration in the basal ganglia. Pathologically this condition differs from PD in that the nigrostriatal pathway is intact, but there is degeneration of neurons in the substantia nigra, pars reticulata and of output neurons in the striatum (Gebbink, 1968). This would result in a reduction in the normal inhibitory outflow of the striatum to the superior colliculus. Although hypometric saccades in the REM paradigm have been found in this condition (Lasker *et al.*, 1988) but not in the RAN paradigm, there is an important difference between the two pathologies. In PD there is no deficit in the ability to suppress a reflexive saccade to the target in the REM paradigm, whereas in Huntington's disease frequent reflexive saccades were observed (Lasker *et al.*, 1987).

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THE ORIGINS OF UTILIZATION BEHAVIOUR

by TIM SHALLICE,[1,2] PAUL W. BURGESS,[1,2] FREDERICK SCHON[3] *and* DOREEN M. BAXTER[4]

(From the [1]Psychology Department, National Hospital, Queen Square, London, the [2]MRC Applied Psychology Unit, Cambridge, the [3]Department of Neurology, Atkinson Morley's Hospital, Wimbledon, and [4]St Andrews Hospital, Northampton, UK)

SUMMARY

Utilization behaviour has previously been described clinically by Lhermitte (1983). An experimental investigation is reported of utilization behaviour in a patient with a localized inferior medial bifrontal lesion. The patient picked up and used irrelevant objects not only when placed directly in front of him—the procedure developed by Lhermitte—but also when he had been instructed to carry out other tasks and his attention had not been directed to the objects. The behaviour occurred most frequently in the brief intervals between tasks, and more often when auditory-verbal rather than visuomotor tasks were being performed. The results are interpreted within an information-processing model of frontal lobe function. A differentiation is made between two forms of utilization behaviour—an 'incidental' form, as exhibited by the patient, and an 'induced' form where it occurs only when Lhermitte's procedure is adopted.

INTRODUCTION

'Utilization behaviour' was first described by Lhermitte (1983) to denote a type of behaviour in which patients appear to grasp and use objects when they are presented to them. The procedure by which this type of behaviour was induced by Lhermitte is quite complex. The examiner and patient are typically seated on opposite sides of a desk. Throughout the examination the examiner remains silent. After eliciting grasping behaviour (Wilson and Walshe, 1914; Adie and Critchley, 1927), the examiner stimulates the palm and fingers of one of the patient's hands with a common object, such as a glass. The object can also be held out and abruptly withdrawn as though to incite the patient to seize it. In either case, a patient exhibiting utilization behaviour will grasp the glass and use it. A second object, such as a bottle of water, can then be introduced in a similar way. After what appears to be a short interval of apparent puzzlement, the patient pours the water into the glass and then drinks it. Other common objects which the patient may be expected to use in normal life (e.g., a cigarette lighter, a dish, a fork, a knife, fruit) then elicit behaviours appropriate to them.

It is not clear from Lhermitte's account how far the behaviour of the examiner influences that of the patient. However, despite the difficulties inherent in the interpretation of such observations, the behaviour itself appears to be abnormal and of localizing significance. Thus Lhermitte reports that in more than 100 normal subjects, this behaviour was never observed. Those patients in whom he elicited utilization behaviour all had

Correspondence to: Dr Tim Shallice, Psychology Department, National Hospital, Queen Square, London WC1N 3BG, UK.

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frontal lobe lesions and he interpreted the behaviour as being the result of an 'imbalance' between impaired frontal and intact parietal lobe processes. In the absence of the inhibitory function of the frontal lobes, the activity of the parietal lobes is released.

Lhermitte's summary statement 'the presentation of objects implies the order to grasp and use them', does, however, suggest an alternative interpretation in terms of the 'demand characteristics' of the situation, namely the social setting that establishes a set to respond in a particular way. Thus the patient, confused by the surprising behaviour of the doctor and knowing that doctors typically present objects to patients for some test purpose, simply thinks that the doctor expects the object to be used! Indeed, this is precisely what Lhermitte's patients reported when questioned about the testing session. Lhermitte argued that this cannot be the actual reason for their actions, as patients were instructed not to touch the objects after the first instance of such behaviour. Nevertheless, after a period of distraction they continued to show utilization behaviour. However, without detailed knowledge of the cognitive status of the patients, it is difficult to assess this alternative explanation for his findings. In Lhermitte's original investigation, limited psychometric results were provided for only one patient, a metallurgist with a WAIS (Wechsler Adult Intelligence Scale) IQ of 70. In view of this man's previous occupation, the overall WAIS results indicate a moderate to marked degree of intellectual deterioration. A later paper (Lhermitte *et al.*, 1986) was primarily concerned with a related condition—imitation behaviour—where the patient without instructions imitates the examiner's gestures; this paper contains some neuropsychological results on patients who show utilization behaviour but only in the form of group means.

In this paper we provide a detailed description of a patient with utilization behaviour which confirms both Lhermitte's observations and the localizing significance of the disorder. We explore the question of whether utilization behaviour is an independent phenomenon or whether it occurs just because of the patient's mistaken interpretation of the doctor's expectations. Our patient, who had focal bifrontal infarcts, exhibited utilization behaviour not only when presented directly with objects but also when he was actively engaged in other tasks and the situation was arranged to discourage the occurrence of the behaviour. Finally, Lhermitte did not investigate the factors influencing whether or not utilization behaviour would be exhibited. We report a study of the predisposing conditions.

CASE REPORT

L.E., a 52-yr-old, right-handed man, employed as a damp-proofing and dry rot operative, developed an acute behavioural disturbance. On September 17, 1987 his son reported that the patient was found early in the morning wearing someone else's shoes, not apparently talking or responding to simple commands but putting coins into his mouth and grabbing imaginary objects. He went round the house, moving furniture, opening cupboards and turning light switches on and off. He had no previous psychiatric history but had suffered lower limb bilateral deep vein thromboses. He smoked 40 cigarettes a day. There was no family history of cerebrovascular disease. After his admission to a psychiatric hospital and subsequent transfer to a regional neurology unit, he was noted to be silent unless questioned. He obeyed simple commands and spoke without apparent dysphasia. He spent long periods of time grinding his teeth. Apart from bilateral manual grasp reflexes there were no neurological or cardiovascular abnormalities and he was normo-

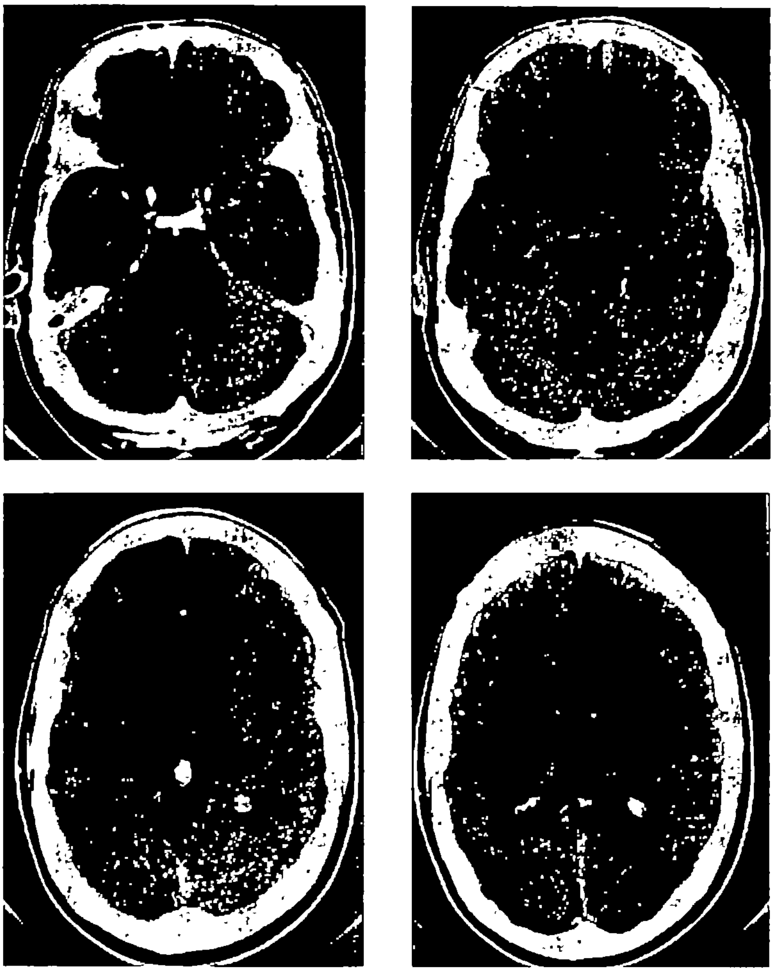

FIG. 1. CT scan showing bilateral inferior medial frontal lesions.

tensive. While in hospital he was incontinent of urine on most days without showing any apparent concern.

Routine blood tests, including serum lipids and treponemal serology, were normal. In view of the past history of deep vein thromboses extensive haematological investigations were carried out, including packed cell volume, ESR, a full autoantibody screen, antithrombin III, protein C and lupus anticoagulant studies, all of which were unremarkable. CSF examination was normal; in particular there was no xanthochromia or excess of red blood cells to suggest subarachnoid bleeding.

A CT brain scan (fig. 1) showed acute ischaemic changes in the inferior and medial aspect of both cerebral hemispheres and the genu and rostrum of the corpus callosum. In addition, on the right side the head of the caudate nucleus with the adjacent internal capsule and putamen were involved; on the left the changes were less extensive but the genu of the internal capsule was involved. The lesions were in the distribution of branches of both anterior cerebral arteries. Carotid angiography revealed complete occlusion of the left proximal anterior cerebral artery just beyond its origin. The right anterior cerebral artery was found to be remarkably hypoplastic, and it was presumed that the basal portions of both frontal lobes were supplied from the left anterior cerebral artery before the thromboembolic event, the exact aetiology of which remained undetermined.

TABLE 1. WECHSLER ADULT INTELLIGENCE SCORES (AGE-SCALED)

Verbal subtests		*Performance subtests*	
Arithmetic	3	Picture Completion	6
Similarities	7	Block Design	9
Digit span	10	Picture Arrangement	3
Vocabulary	4		
Verbal IQ = 73		Performance IQ = 79	

Some clinical improvement occurred during the 6 months after his stroke when the present investigation was undertaken. In particular there was a reduction in his urinary incontinence. However, he had been unable to return to work and still needed careful supervision to prevent him using domestic equipment in an unsafe fashion. If left to himself he would, for instance, continually make tea if he saw tea bags. He tended to act like a young child turning taps on and off, playing with ornaments, opening and closing doors and even playing with some of his grandchildren's toys.

L.E. was referred to the National Hospital for neuropsychological assessment and seen on three occasions (October 12, 26, November 16, 1987). His performance on the WAIS is shown in Table 1. He achieved a verbal IQ of 73 and a performance IQ of 79. Individual subtest scores ranged from very defective on Arithmetic and Picture Arrangement to average on Digit Span. His reading IQ, as estimated from the Schonell Graded Reading Vocabulary Test (Schonell and Schonell, 1950), predicted a dull average optimal level of 88 (Nelson and McKenna, 1975) which suggested only mild intellectual deterioration on the WAIS.

His performance on both spatial and perceptual tests was intact: fragmented letters, 18/20; cube analysis, 12/12; dot centre, 20/20 (Warrington and James, 1988); Rey Osterrieth copy, 33/36 (Taylor, 1959). His praxic skills were also intact and he was able to initiate simple hand movements quickly and efficiently with either hand.

He spontaneously said little but in response to questions his expressive speech was fluent with normal prosody and sentence length; paraphasias were not observed. On the Oldfield and Wingfield (1965) naming test he named 25/30 pictures. On a more stringent graded naming test (McKenna and Warrington, 1983) he consistently scored within the dull average range, a level commensurate with his estimated optimal level (8/30, October 12; 9/30, November 16). The intact naming and his ability to produce sentences *other* than those he hears—for instance in describing the Boston Cookie Jar picture (Goodglass and Kaplan, 1972)—places the reduction in his spontaneous speech in the domain of a dynamic aphasia rather than a transcortical motor aphasia. On the Peabody Picture Vocabulary Test (Dunn, 1965) he scored 83/150 (October 12) and 107/150 (prorated) (November 16) at IQ levels 74 and 96, respectively.

A variety of memory tests were administered and his performance was very weak on all these tests. Thus he scored at chance level (Camden A = 13/30) on a very easy recognition memory test which used distinctive coloured photographs and a forced-choice response of three alternatives (E. K. Warrington, personal communication). On the Wechsler Paired Associate Learning subtest his score of 4½ was entirely the result of his success on easy items. His 10 min delayed reproduction of the Rey Osterrieth figure showed little or no relationship to the original drawing (5½/36). Recall of the short story in the Coughlan and Hollows (1984) Memory Battery was very poor (1 min 6/56, <10th percentile, delayed 0/56). On direct questioning he was disorientated in time and place and confabulated in a 'provoked' rather than 'spontaneous' fashion (Kopelman, 1987). Thus, when asked, he once claimed that the examiner's office was a room at work.

Two of Willison's (1988) 'alertness' tests were given to E.L. (*see also* Willison *et al.*, 1980). On the speed of copying 6 lines of 10 digits he was very slow (73 s; <5th percentile). Moreover, he made 6 errors, all of them on the last 2 lines. He was even worse at the complementary test of cancelling 0s on a sheet of digits; the test was abandoned half-way through afer 2½ min (<1st percentile).

On all frontal lobe tests his performance was grossly impaired. He failed the Weigl (1941) Sorting Test and a simple alternation problem (Chorover and Cole, 1966). The Tower of London test (Shallice, 1982) was abandoned at the halfway stage because of his continual rule violations. On Verbal Fluency (Goodglass and Kaplan, 1972) he produced 3 words beginning with F in 60 s, and 4 with S; for the letter A he produced only names despite repeated instructions that they were not appropriate.

In summary, L.E.'s performance on spatial, perceptual, language and simple praxic tests was satisfactory. By contrast his performance on tasks that involved a frontal or long-term memory component was uniformly and severely impaired.

EXAMINATION OF UTILIZATION BEHAVIOUR

L.E. exhibited utilization behaviour when examined clinically using the procedure developed by Lhermitte. In addition, in two sessions utilization behaviour also occurred with a different procedure. He was tested on neuropsychological tasks in the presence of a variety of objects each of which could act as a vehicle for utilization behaviour, the sets of objects being available on the two ends of the testing desk. This procedure was employed to investigate whether utilization behaviour would occur in a situation where there was no explicit or implicit expectation that the objects should be used. No explanation was volunteered to the patient regarding the presence of the objects on the ends of the desk, and the subject made no reference to them at any point.

First incidental procedure

The session began with general conversation between the examiner and the patient. This was followed by a brief clinical interview and the administration of a set of 'frontal' and naming tasks. The session ended with further questioning by the examiner.

Results

Twenty-three occurrences of incidental utilization behaviour were observed and categorized as follows.

Type 1. 'Toying' (8 instances). This was defined by a single action in which an object was manipulated but not in a purposeful way or in the way it was originally intended to be used (e.g., picking up a pencil but not using it for any purpose; idly pushing a stopwatch around the table top).

Type 2. 'Complex Toying' (2 instances). This class of actions involved 2 objects used in a linked way but in an incomplete fashion or not for the purpose for which they were both designed (e.g., picking up a pencil and using it to move the Weigl shapes).

Type 3. 'Coherent Activity' (13 instances). This classification was used when a set of actions was integrated in a typical fashion with respect to the relevant objects (e.g., picking up a pen and paper and writing; unscrewing an electric plug with a screwdriver; spontaneously picking up a pack of cards and dealing 4 cards to himself and 4 cards to each of the two examiners present).

Utilization behaviour occurred not only when L.E. was in conversation with the examiner, but also when he was in the middle of performing both verbal and nonverbal neuropsychological tests (for example, the Weigl Sorting Task, Cognitive Estimates (Shallice and Evans, 1978), Tower of London). Thus he took the playing cards and dealt them while attempting to explain some common proverbs, albeit in a very concrete fashion.

Second incidental procedure

In a later paper Lhermitte (1986) has argued that utilization behaviour is one aspect of the so-called 'environmental dependency' syndrome in which patients without instructions respond in complex social situations as though they have a specific role. If L.E.'s utilization behaviour were to be explained in this way he would be expected to use objects concordant with the situation in which he found himself more than ones that were not concordant.

On a separate session 'incidental' utilization behaviour was investigated while L.E. was being tested in the presence of objects placed on trays; each tray contained 5 'congruent' and 6 'incongruent' objects.

The classification of concordance was made by the authors before the experiment according to whether an object could reasonably be expected to be present on an office desk or not; a pencil or a ruler would be congruent but a toy gun or a candle would not be expected to be there.

The session consisted of three separate sections which succeeded each other without breaks. The first part was a factorially designed experiment in which three other factors potentially relevant to utilization behaviour were manipulated. In the second and third parts the utilization objects remained available to obtain more data on the effects of congruency; the tasks used were chosen to provide an alternative attentional focus and to make relatively few structural demands so that utilization behaviour could potentially occur at the same time as they were being carried out.

1. *Experimental section.* This was designed to explore the effects of the following factors in a systematic way. (1) Proximity—two trays were on the table at any one time. The trays were either placed *near* the patient (approximately at a distance of 8 cm (near hand) 15 cm (far hand) or far from the patient (approximately at a distance of 26 cm (near hand) 29 cm (far hand)). (2) Location—one tray was placed to the left and one to the right of the patient. (3) Patient activity—an equal number (4) of auditory-verbal, visuoverbal and visuomanual tests were administered. All the tests lasted 5 min.

Two pairs of trays were used. The pair of trays, the proximity and the three types of patient activity were varied across the 12 tasks using a counterbalanced design.

2. *Clinical interview section.* The patient was asked about his family and work in an interview lasting 15 min. A particular pair of trays was continually present, one near left and the other near right.

3. *Verbal test section.* A series of tests was carried out all requiring auditory input and spoken output (e.g., verbal fluency, proverbs, WAIS similarities and arithmetic). Three trays were continually present, 2 to the patient's left and 1 to his right, 3 being used to increase the physical potential for utilization behaviour to occur.

Results

An instance of utilization behaviour was defined as any action with 1 or more objects on a tray which lasted more than 1 s and which followed the end of a previous instance by more than 1 s. The identification was made by 2 of the examiners taken from a videotape recording of the whole session. There were 31 examples of incidental utilization behaviour. In this second incidental procedure there were fewer instances of coherent activity (3) than in the earlier test session (13). They involved (1) picking up the candle, checking to see if matches were present then using them to light the candle (twice) and (2) selecting and lighting a cigarette.

The congruency of the stimuli to the environment had little or no effect on the incidence rate. Thus overall 5 behaviours involved both types of stimuli and there were 14 instances involving the congruent stimuli and 13 involving the incongruent ones; the relative frequency of use of congruent and incongruent objects did not differ from chance (binomial test compared with chance value of 0.45, 0.55, $P > 0.2$). Certain particular stimuli appeared to elicit utilization behaviours relatively frequently (e.g., toy gun, ruler, paint colour samples, candle), but there appeared to be no particular relation to the object's congruency. Of these frequently used objects only the paint colour samples were at all visually striking; thus the most used object, the toy gun, was small and gun-metal grey. Neither of the physical factors investigated in the experimental section appeared to be a critical determinant of the occurrence of utilization behaviour. Six behaviours occurred when the trays were in the 'near' and 3 in the 'far' position. (One behaviour was not considered as the object had previously been moved and left in an atypical position by the patient.) Overall, L.E. selected objects to his right slightly more than those to his left although the difference was not significant (right = 60%; left = 40%).

The one factor which seemed to have a major effect on the incidence of utilization behaviour in section 1 was the type of task. No utilization behaviour occurred either when a visual-verbal or a visual-manual task was being performed, but there were 3 instances when an auditory-verbal task was being carried out and 7 instances of a behaviour being initiated in the very short intervals between tasks, a small percentage of the total time.

Differential task demands would also explain the striking difference in rate of occurrence of utilization behaviours across the three sections which was apparent on a post hoc analysis of behaviour across the whole session. Intervals between successive episodes of utilization behaviour differed greatly between the different sections (Kruskal Wallis, $H(2) = 13.02$, $P < 0.005$) (*see* fig. 2). The incidence rate was significantly higher during the clinical interview than when formal tests were being carried out. Thus post hoc analysis showed a significant difference in rate between sections 1 and 2 (Newman-Keuls, $P < 0.01$), and between 2 and 3 (Newman-Keuls, $P < 0.05$) but not between 1 and 3 (Newman-Keuls, n.s.). In the clinical interview (section II) utilization behaviours occurred during questioning. When verbal tests were presented in section III, utilization behaviours occurred between tasks on 2 occasions and there were 4 instances during the auditory-verbal tasks. Thus all examples of utilization behaviours occurred when L.E. was supposed to be carrying out auditory-verbal tasks or, with a higher incidence rate, between tasks. Finally, there was a statistically significant more frequent occurrence of the behaviours in the second section of the session than in the third. As the third condition was the one where objects were physically the most available, this finding means that fatigue or familiarity with the situation can hardly be the dominant factor.

On 2 occasions during the session it was arranged for the telephone to ring and for the examiner not to answer it immediately. On one occasion the patient, who was the same distance from the telephone as the examiner, answered it himself after only a brief pause, confabulated in reponse to a query and then began to act on the basis of the confabulation. On the second occasion he did not answer it.

DISCUSSION

We have described a patient, L.E., who exhibits utilization behaviour when objects are presented to him without instructions, the condition described by Lhermitte. In addition the behaviour occurred when irrelevant objects were 'incidentally' present on the testing desk. It occurred more floridly on the first of the two 'incidental' testing sessions but was still clearly present on the second. The utilization behaviour was present in the absence of confusion or dementia. Indeed L.E.'s overall IQ was only mildly

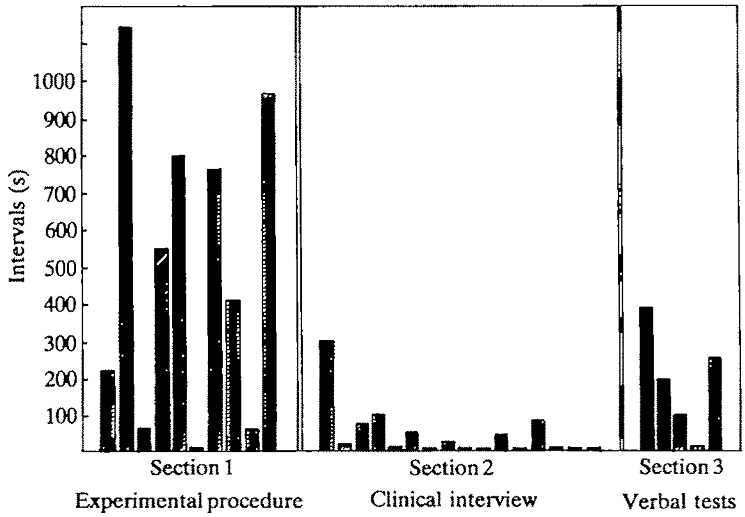

FIG. 2. Each bar represents the interval between the end of one utilization behaviour and the beginning of the next. The three sections correspond to the three of the testing session.

depressed in comparison with his estimated optimal level. His naming, perception, spatial and simple praxic skills were intact but his performance was markedly impaired on all tests of memory, those of mental speed, and those that involved frontal lobe functions.

The lesion as determined by the CT scan is in accord with Lhermitte's general characterization of the anatomical basis of the disorder. Lhermitte's patients all had frontal lobe damage due to a wide variety of causes, including a ruptured anterior communicating artery aneurysm, a left frontal arteriovenous malformation, a ventricular tumour, an extensive right hemisphere infarct and a right frontal glioma. However, although Lhermitte suggested that utilization behaviour resulted from lesions of the orbital surface of the inferior frontal lobes and possibly the head of the caudate nucleus, in most intances the patients had much more extensive lesions. None had such localized pathology as the present patient, which showed localized areas of inferior bifrontal infarction together with some involvement of the basal ganglia. This unusual infarct distribution presumably arose from a congenital anomaly in the circle of Willis. The CT scan appearances suggested the possibility of vasospasm secondary to rupture of an anterior communicating artery aneurysm, but this was excluded by the normal CSF and the angiogram.

Lhermitte provides two alternative explanations of the behaviour—one phenomenological and one neuroanatomical. In the former he states that '. . . tactile, visual-tactile or visual stimuli imply to the patient an order *to grasp the objects presented and to use them* (his italics). Observation of the behaviour of these patients is instructive in this respect: the stage when they hesitate and do not use the grasped objects; the stage when, after a moment of hesitation, they use them; the stage when, without hesitation, they use them at once'. The major obstacle to such an interpretation relates to the demand characteristics inherent in Lhermitte's testing procedure. The patients may misunderstand the requirements of the situation and believe they *ought* to show how to use the objects. This possibility is particularly relevant when background neuropsychological test data are not available for a patient.

This possibility is not a purely theoretical one. We have observed 2 additional patients who manifested utilization behaviour clinically but who had lesions with quite different locations. Both had left parietotemporal lesions and a consequent aphasia. One of these patients was tested more extensively and 'clinical' utilization behaviour stopped after he was instructed not to touch the objects. Moreover, unlike L.E., he did not show utilization behaviour in the 'incidental' condition where objects were available on the desk when cognitive tests were being carried out. In these cases the most plausible explanation is that the patients were compensating for more general comprehension difficulties by guessing the intentions of others. As a result they acted atypically, based on their interpretation of the requirements of the testing situation. Whether analogous interpretations can occur in patients without primary language problems remains open. It should be noted, however, that at least 1 of Lhermitte's 5 cases was aphasic.

By contrast, an interpretation of this sort can be excluded in L.E. During the two 'incidental' testing sessions the attention of the patient was never drawn to the objects by the investigators. Moreover, during both of these sessions the behaviour occurred both when the patient's attention had been directed to a specific task and also at times when he was actually carrying out other tasks. Yet utilization behaviour frequently occurred.

Lhermitte's neuroanatomical account of utilization behaviour is based on the theoretical views of Denny-Brown (1958) on a possible imbalance between the activities of the frontal and parietal lobes. Visual input from environmental stimuli activate parietal lobe systems which in turn initiate actions. This process is normally modulated and inhibited by frontal lobe systems: specific damage to the frontal lobes will lead to the unmodulated effects of the parietal systems being observed and, given an appropriate environment, utilization behaviour will result.

A close analogy can be drawn between this neuroanatomical account and the functional model of the control of action and thought developed by Norman and Shallice (1986) to explain both normal studies of attention and also the performance of patients with frontal lobe disorders (Shallice, 1982). The model involves a number of different levels and contains four types of component (1) special-purpose cognitive subsystems, (2) schemata, (3) contention scheduling, and (4) the supervisory attentional system (*see* fig. 3). So in a skill like driving, many cognitive subsystems are required—object recognition, spatial processing systems, manual control and so on. They are the types of subsystem selectively damaged after lesions to more posterior cortical systems. The schemata may be thought of as analogous to programs that 'run' on these cognitive subsystems. Thus in a skill like driving, the procedures for controlling appropriate behaviour at traffic lights, for overtaking, for turning left and so on each consist of a schema or, more usually, a hierarchically organized set of schemata. The highest level is that of the largest 'routine' unit of behaviour, the lowest would be that of the control of the movement of head and eyes to look in the mirror.

Each schema is activated by 'triggers'—relevant perceptual input or the outputs of other operative schemata. The sight of a red traffic light triggers slowing or braking depending on its distance; if the overtaking schema becomes operative this leads to the mirror-consulting schema becoming activated. At any particular time many schemata may be activated. Contention scheduling is the mechanism by which appropriate schemata are selected to control behaviour, primarily through schemata being in a mutually inhibitory relation where there is an overlap in the cognitive subsystems they typically require.

It is argued on the theory that in addition to the first three types of component the cognitive system contains a Supervisory System which standardly has a monitoring function. It comes positively into play in nonroutine situations where novel responses are required. This occurs when schemata selected in contention scheduling fail to provide an appropriate response, or when the stimulus situation is such as to leave all schemata only weakly activated as no appropriate response has been learned. Consider how you respond when a warning light comes on when you are driving: the action you take depends on reflecting on the specific circumstances. The Supervisory System is held to operate much more slowly and its activity does not lead directly to a response; instead it provides

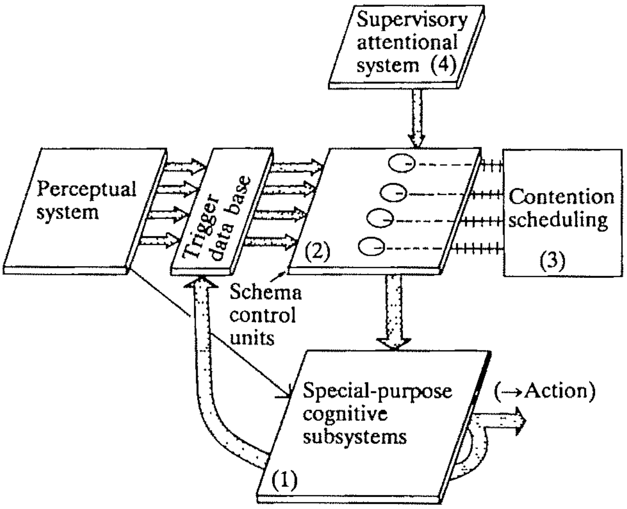

FIG. 3. The Norman-Shallice model of action control. Dotted lines represent activating input, hatched lines represent the primarily inhibitory function of contention scheduling.

additional activation or inhibition for schemata, so altering their chance of being selected in contention scheduling. It is thought to be located in the frontal lobes.

An account of the characteristics of utilization behaviour can be given from this perspective. First, in the absence of a working Supervisory System in the frontal lobes, perceptual input alone can lead to activation of an action schema and to its selection in contention scheduling; for instance, the sight of a pair of scissors and paper activates the actions associated with the objects, and these behaviours are then carried out (selected) in the absence of supervisory inhibition. This is precisely what happens in utilization behaviour. When the Supervisory System is operative the possibility of this happening is greatly reduced: supervisory activation of relevant schemata leads to the inhibition of the irrelevant ones, which are being randomly triggered by perceptual input. Thus whenever we work at a task, there are a variety of stimuli in our line of vision or within our hearing, irrelevant to the task at hand. In order to concentrate and carry out the task efficiently schemata activated by this input must be inhibited.

Secondly, even when the Supervisory System is impaired—as can be assumed for L.E.—the probability of utilization behaviour occurring will depend on whether any action schema which is being randomly triggered in contention scheduling is or is not being inhibited by an already active schema. This is more likely when the patient has been instructed to carry out a task and task-irrelevant stimuli are being presented. The model would predict that utilization behaviour should occur most frequently in a patient with an impaired Supervisory System when no task is being undertaken. Utilization behaviour should also be more frequently observed when the required task is in the auditory-verbal domain, when there would be no overlap in the cognitive subsystems involved, than when a task-relevant visual input is competing with the triggering stimuli.

Such a model provides a more articulated version of Lhermitte's general position and predicts differences in the frequency of utilization behaviour according to the particular activity the patient is performing. It fits the pattern of results found in our patient L.E.

On this account why should L.E. be able to carry out certain psychometric tasks satisfactorily? There are various reasons why this should be so. First, a number of tasks on which he performed well, such as Cube Analysis or Fragmented Letters, are untimed; they are therefore less sensitive to the occurrence of an episode of utilization behaviour since attention can be refocused on the task after a gap and an adequate score achieved. Secondly, tasks which require a fairly continuous and changing motor output, like copying the Rey-Osterrieth Figure, tended not to be affected by utilization behaviour; the schemata controlling them are presumably fairly continuously and strongly activated and so inhibit randomly triggered action schemata. Thirdly, certain of the psychometric tasks—particularly the auditory-verbal ones such as Digit Span—on which he performed well, consist of a number of individual trials which are both very short and initiated by an attention-catching spoken input from the examiner. By contrast, in tasks such as Willison's mental speed tests, where a display which has to be scanned does not change until the repetitive task which takes many seconds is completed, an interruption would be likely to occur; indeed such tasks were performed very poorly.

In this paper we have considered two explanations of utilization behaviour. First, we discuss the behaviour in terms of an absence of a Supervisory System associated with impaired frontal lobe functions, consistent with Lhermitte's neuroanatomical model. Secondly, we discuss it in terms of the 'demand characteristics' of the situation. Lhermitte's procedure does not allow a distinction to be made between these two explanations. To what extent one or the other is appropriate for the range of patients who exhibit utilization behaviour with Lhermitte's procedure remains to be determined. Our observations suggest that the utilization behaviour that takes place when objects are directly presented to patients can occur for either of these reasons. In particular, utilization behaviour can occur not only when objects are presented directly to patients but also more importantly when they are placed near patients in situations where they are instructed to carry out other tasks. The first form would be induced utilization behaviour and the second incidental utilization behaviour. The location of the lesion in the present patient was in accordance with Lhermitte's claim that utilization behaviour has an inferior frontal localization.

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SENSORIMOTOR DISTURBANCES IN PATIENTS WITH LESIONS OF THE PARIETAL CORTEX

by MAX PAUSE, ERWIN KUNESCH, FERDINAND BINKOFSKI *and* HANS-JOACHIM FREUND

(*From the Department of Neurology, University of Düsseldorf, FRG*)

SUMMARY

Somatosensory and motor disturbances of hand function were examined in 9 patients with parietal lobe lesions. A quantitative score was used for the elaboration of sensorimotor profiles displaying the relative degree of functional impairment. In patients with anterior parietal lobe lesions somaesthesis was clearly more disturbed than motor function. Simple aspects of somaesthesis (surface sensibility, two-point discrimination, position sense) were disturbed to about the same degree as complex somatosensory (tactile recognition) tasks. On the other hand, patients with lesions of the posterior parietal lobe showed preferential impairment of complex somatosensory and motor functions (exploratory and manipulative finger movements).

In 4 patients, analysis of motor behaviour by means of an optoelectronic system showed that reaching, formation of hand aperture and target acquisition were less disturbed than manipulative behaviour. Finger movement trajectories during dynamic digital palpation of objects were grossly deranged in the patients with posterior parietal damage. The temporal characteristics of the finger movements during active touch were completely destroyed. This leads to a breakdown of the finely tuned digital scanning process required for the sequential sampling of mechanoreceptive information. Remarkably, these patients could produce the exploratory finger movements imitatively. The motor disability of the parietal hand does not lie in the loss of the kinetic memory to perform these movements, but in the loss of their evocation by appropriate sensory stimuli. This deficit is not due to a lack of somatosensory information because that may be relatively well preserved. It is concluded that the motor disturbance in posterior parietal lobe disease lies essentially in the conception and execution of the spatiotemporal movement patterns necessary to bring those receptors into action which would normally provide the information about tactile objects. This illustrates the intricate mutual dependence of the spatiotemporal organization of receptor activation by movement and of the formation of movement trajectories on the basis of adequate sensory processing.

INTRODUCTION

It is a widely held view that the sensory deficits after parietal lobe damage resemble those seen in patients with lesions of the posterior columns (PC). This similarity was initially described by Dejerine (1914), Stein and von Weizsäcker (1927, 1928) and Delay (1935). Head and Holmes (1911) and Head (1918) regarded the PC input as a major constituent of parietal lobe function. This view was corroborated by Wartenberg (1939) and Bender *et al.* (1982) who considered the loss of the recognition of forms traced on the skin as probably the most specific deficit for damage of the PC. Dejerine and Mouzon (1915) emphasized the preponderance of the impairment of postural sensitivity, of tactile discrimination, of the precision of the localization of stimuli on the skin and

Correspondence to: Professor H.-J. Freund, Neurologische Universitätsklinik, Moorenstrasse 5, D-4000 Düsseldorf, FRG.

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of stereognosis with only minor impairment of protopathic sensibility, in particular pain and thermal sensation.

As pointed out by Wall and Noordenbos (1977) the above-mentioned inferences about the characteristic functional deficit after PC lesions were based on a few well documented reports on postmortem findings only. Nathan *et al.* (1986) have conducted an extensive clinicopathological correlation on the basis of their own patients and a review of some earlier neglected case descriptons (Gans, 1916; Puusepp, 1933; Kroll, 1930; Cook and Browder, 1965). They concluded that light touch and pressure were not lost after PC lesions but that any kind of discrimination, as well as the detection of movements and position, were disturbed. These clinical observations are in agreement with lesion studies and with morphological and neurophysiological data from nonhuman primates. Mountcastle's (1984) distinction between 'simple' and 'complex' aspects of somaesthesis corresponds to the traditional clinical categories of protopathic and epicritic sensibility that was attributed to the spinothalamic and lemniscal projection systems.

In contrast to the disturbance of discrimination between different surface textures and object forms as a consequence of a disruption of afferent somatosensory information, Critchley (1953) showed that astereognosis may occur as a deficit of mental operation without any concomitant sensory disturbance. Such cases were seen after parietal lobe damage, thus representing a cortical perceptual dysfunction clearly different from that observed after PC lesions. In most patients, however, the somatosensory impairment following parietal lesions was very similar to PC dysfunction. The role of previous experience for gnostic functions was emphasized by Dejerine (1907) for cases with infantile hemiplegia, where astereognosis was found in the paralysed hand without any detectable sensory changes. Dejerine coined the term 'virgin hand' in order to point out that the sensory disorder was an astereognosis through ignorance, as the hand had never been employed as a palpating organ. A contrary phenomenon was observed by Critchley (1953) in a patient with Apert's agyrocephalosyndactyly who had congenital rudimentary hands with no free phalanges but stumped and deformed metacarpals. An attenuated thumb was freed by plastic surgery, allowing the patient to acquire an unexpected degree of dexterity with the stumps. As soon as he could use the hand he revealed a high level of texture recognition and tactile discrimination comparable with that present in a normal person.

An extensive quantitative study relating the psychophysically measured somatosensory deficits to the site of brain lesions was conducted by Roland (1987). He presented evidence that lesions at different sites in the parietal lobe were associated with a differential involvement of the various complex somatosensory functions. Lesions of the anterior deep part of SI were associated with a disturbance of the detection of passive movement, kinaesthesia and the detection of size and shape exclusively on the contralateral side. Lesions of the somatosensory association areas also led to the contralateral discrimination loss. The results further suggested that the anterior part of SI participates in the initial demodulation of macrogeometric and kinaesthetic signals, whereas the overt part of SI participates in the reconstruction of curvature and microgeometric surface characteristics, and of kinaesthetic signals from the skin. The lack of correlation between kinaesthesia and size and shape thresholds was regarded as evidence that kinaesthesia was too inaccurate to account for shape and size discrimination.

Ablation studies on nonhuman primates have not provided conclusive evidence with respect to the consecutive dysfunctions. Ablation of the posterior parietal cortex either led to severe tactile impairment (Ruch and Fulton, 1935; Ruch *et al.*, 1938; Wilson, 1957; Bates and Ettlinger, 1960; Ettlinger *et al.*, 1966; Moffett *et al.*, 1967; LaMotte and Mountcastle, 1979), or normal left tactile function (Semmes and Turner, 1977). Murray and Mishkin (1984) found that both texture and shape discrimination learning was impaired after ablation of SII. Ablation of area 5 led only to an elevation of the threshold of roughness discrimination. More severe tactile deficits were only observed when the excisions included the posteromedial part of the hand representation of area 2.

In relation to motor deficits, it was noticed from the earliest reports that lesions of the PCs (Gans, 1916) or parietal lobe (Verger, 1900; Head and Holmes, 1911; Dejerine, 1914; Kleist, 1934; Delay, 1935) led to severely clumsy and inappropriate movements and to incompetence in the use of the hands. Excisions of the postcentral gyrus led initially to a complete anaesthesia, areflexia, hypotonia and to a paresis of the contralateral side (Foerster, 1936). In contrast to cases with lesions of the precentral gyrus, the patients could perform voluntary movements immediately after surgery, although these were clumsy and slower than normal. The major motor deficits resembled those described after deafferentation: postural instability, ataxia, the assumption of dystonic postures and loss of smoothness and accuracy of movements performed without visual guidance. Fine movements such as buttoning, writing, drawing and prehension of small objects were severely disturbed. Foerster called this mostly transient deficit 'Tastlähmung' (tactile paresis). Wernicke (1889) emphasized that in cases with postcentral lesions not all motor disturbances could be attributed to the sensory deficits because sensibility was sometimes only slightly impaired. Klein (1931) and Pötzl (1937) used the term 'tactile apraxia' for the disturbance of hand function characterized by preservation of intransitive, expressive and symbolic movements, whereas the exploration and manipulation of objects was grossly disturbed. In some cases exploratory movements of the fingers did not take place at all when an object was put into the hand. Delay (1935) regarded differences between astereognosis and tactile apraxia as representing a quantitative rather than a principal difference. Recently quantitative investigations about the effects of complete peripheral deafferentation (Rothwell *et al.*, 1982; Sanes *et al.*, 1985) or parietal lobe damage (Jeannerod *et al.*, 1984) on motor performance have demonstrated how severely motor function can be disturbed.

The objective of this article is the quantitative evaluation of the motor deficits in 9 patients with parietal lobe damage and their comparison with the type and severity of the somatosensory deficits. The results show that cases with posterior parietal lobe lesions may have major disturbances of motor functions of the hand, including instances when this cannot be accounted for by somatosensory deficits.

METHODS

Data obtained from a detailed clinical examination of 9 patients with unilateral parietal lobe lesions along with quantitative tests of the somatosensory and motor deficits of the hand were compared with the site and extent of the lesions, as revealed by a three-dimensional reconstruction of the CT images. All patients were examined after remission of the initial transient deficits. The aetiology of the lesion was an ischaemic infarct in 7, haemorrhage in 1 and brain damage in early childhood in 1.

Quantitative measurements

These included, for simple somatosensory functions, light touch with von Frey hairs at the fingertips, static two-point discrimination with compasses at the fingertips, successive two-point discrimination as tested by Semmes *et al.* (1960), joint position sense (JPS) by measurement of the angle at the interphalangeal joints, the wrist and the elbow, and vibration sense (VS) using a tuning fork at 128 Hz at the fingertips, distal forearm and elbow. For measurement of complex somaesthesis the recognition of surface textures was tested. A brush, cloth, sandpaper, sponge, rubber, wood, cork, stone, metal, and glass were felt by active touch, the fingertips being moved actively across the test surface (10×6 cm). Tactile recognition of object shape was examined by digital exploration of 20 haptic objects (key, nut, toy marble, India rubber, toy car, small bottle, pencil sharpener, paperclip, screw, wrench, tweezers, cube toy brick, nut, bottle cap, matchbox, small spoon, triangular toy brick, 'bridge' toy brick, small tube, stopper). The objects were first placed on the palm of the hand contralateral to the lesion behind a screen to exclude visual control. After recognition or after 30 s the object was put into the other hand to exclude a general cognitive deficit. With the unaffected hand all patients were able to recognize the above listed objects without exception.

In order to assess complex sensibility a visuotactile matching task was also employed. Two sets of 5 cubes (5×5 cm) with different cues (either bevelled edges, corners or grooves in different positions) were photographed in an unequivocal position and the slide was projected onto a screen. While the patient watched the slide, one of the cubes was placed in the palm of the affected hand behind a concealing screen. After 30 s, no matter whether recognition was achieved or not, the cube was transferred to the unaffected hand where it was correctly identified in most cases. The most difficult task for cognitive sensibility was the recognition of relief figures with elevated lines (3 mm width, 3 mm elevation) mounted on a flat plate (10×10 cm). If possible the patient followed the elevated line with the fingertip. Ten figures were tested (circle, triangle, square, star, the letter M, bottle, rhombus, heart, arrow, hand), first with the affected hand and, if recognition was not successful, with the unaffected hand. The most difficult figures (bottle, hand) were sometimes not recognized with the unaffected hand. Handedness was judged according to the patients' reports about use of the hands in writing, throwing and fine manipulation prior to their disease.

Motor testing is described in Results. In 5 patients (Cases 1, 3, 4, 7, 8) hand movements were recorded by an optoelectronic system (Selspot II) using light-emitting diodes (LEDs) powered by a LED control unit and monitored by two infrared cameras. The frame rate of the system was 100 Hz. Before data acquisition actual LED positions were monitored on a VT 125 terminal providing both real time and graphic display of data.

CASE REPORTS

A brief outline will be presented for each patient, including a description of the major deficit on general neurological examination. Precise sensorimotor profiles will be given in the subsequent section. The site of the lesion is shown for each patient in fig. 1.

Case 1

U.E., female, aged 60 yrs, left-handed. This patient was repeatedly treated with anticoagulants for mitral valve stenosis. She suffered a stroke 16 months before admission. At the first examination after her stroke she had a left hemiparesis and hemianaesthesia. At the time of testing the hemiparesis had improved, the

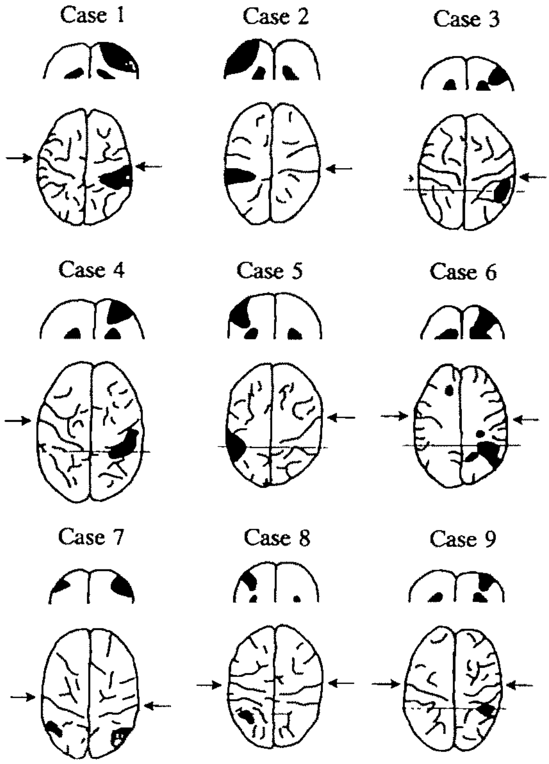

FIG. 1. Drawings of cortical lesions of the patients examined reveal the cortical extent of CT hypodensities (shaded areas). Surface views were constructed from subsquent horizontal CT scans that were 9 mm apart and show the full extent of the cortical lesions as if the brain were viewed from the top. For this purpose the convex aspects of the individual brains were reconstructed by continuation of the sulci on sequential scan planes. The cortical parts of hypodense areas of the different CT planes were then drawn onto the reconstruction of the convexity. The identification of sulci followed the atlas of Matsui and Hirano (1978) and its specification by Ebeling *et al.* (1986). The subcortical extent of the lesion was plotted on the coronal plane on which it was largest. Arrows indicate the central sulcus. Anterior lesion areas shown in the *upper row*, combined lesions in the *middle* and posterior lesions *below*. Three patients had more than one lesion.

muscle tone was normal, the tendon reflexes were increased on the left but the hemianaesthesia had persisted. Sensory testing revealed anaesthesia of the left hand and forearm for all modalities including JPS, VS and stereognosis. Proximal to the elbow she could only perceive strong stimuli of long duration. She could use the left hand for most purposes, and could knit as long as visual control was provided. Without vision all movements decomposed and became ataxic. Reading was normal, but there was marked static ataxia and deficient force control. Neuropsychological tests were normal. CT scans showed an infarct involving the entire right postcentral gyrus.

Case 2

W.I., female, aged 49 yrs, right-handed. A few hours before admission she had developed an acute right brachiofacial hemiparesis and became unable to speak. On admission she had a severe Broca aphasia, an angular gyrus syndrome and a right hemiparesis. Sensibility could not be assessed adequately. Four months later she was again admitted with a deep vein thrombosis in the right leg. At this time a moderate Broca aphasia was still present but verbal communication was sufficient for full testing with our repertoire.

Sensory testing showed a severe hypaesthesia of the right arm with postural instability and disturbed force control. JPS was moderately reduced but VS was normal. The hemiparesis had almost completely resolved. Muscle tone was normal but the tendon reflexes were mildly accentuated on the right. All movements with the right hand were slow; reaching was normal. She was not able to perform an alternating windmill movement with both arms but could rotate each arm independently. Angiography demonstrated an occlusion of the left internal carotid artery. The CT scan showed a left anterior parietal infarct. Further remission was very slow.

Case 3

P.K., female, aged 69 yrs, right-handed. Symptoms began 6 weeks before admission, when she noticed that she misreached for a cigarette box and offered an empty left hand without realizing her mistake. From that time on she was aware of severe clumsiness of her left hand, which improved only slowly. On admission, she presented with left hemihypaesthesia with absent JPS of the fingers, complete astereognosis in the left hand and visual and somatosensory neglect to the left, and a mild constructional apraxia with the right hand. Vibration was normal. Force and muscle tone were normal; the tendon reflexes were slightly increased on the left. Movements of the left hand were slow, and there was marked postural instability and disturbance of force control. Exploratory movements consisted almost exclusively of opening and closing the fist, with frequent loss of objects which were dropped unnoticed. Reaching with the left hand was inaccurate and she frequently could not grasp the object even under visual control. CT scans showed a right temporoparietal infarct. Angiography demonstrated severe generalized arteriosclerotic changes. The patient died shortly after discharge. Postmortem examination confirmed a right parietal infarct extending from the postcentral gyrus to the lobulus parietalis superior, involving the grey matter and extending 3 cm deep into the white matter.

Case 4

D.L., male, aged 59 yrs, right-handed, had developed an acute stroke with a severe left hemiparesis and hemihypaesthesia 7 months before admission. Following the initial hemiplegia there was a gradual recovery and after 7 months his grip had returned to normal. In spite of this, his left hand was useless for any purpose. On examination, he had dystonic postures of the left hand and arm with mildly increased muscle tone and tendon reflexes on the left, and an almost complete loss of all somatosensory modalities as well as complete astereognosis. Reading was normal. He had severe postural instability and impaired force control. Despite physiotherapy he scarcely improved, so that his left hand remained useless. His initial stroke was caused by a haemorrhagic infarct of the right pre- and postcentral gyri. A follow-up CT scan 7 months later showed an infarct of the right postcentral gyrus extending into the white matter underlying the precentral gyrus.

Case 5

D.G., male, aged 49 yrs, left-handed. This patient had been repeatedly admitted with generalized seizures due to birth trauma leaving a left temporoparietal cystic scar. Ever since he could remember he had had clumsiness of the right hand. There was a mild hypaesthesia of the right arm and hand with mildly reduced JPS and stereognosis and normal VS. Muscle tone and tendon reflexes were normal. Fine movements with the right hand were slow and clumsy but not paretic. He was able to catch a ball with the right hand and to throw it normally. Reaching was normal. Repeated CT scans showed a left temporoparietal hypodense area that had remained unchanged for many years. He performed manual work in a factory.

Case 6

W.I.I., female, aged 69 yrs, right-handed. A few days before admission she had noticed frequent misreaching with her left hand and restricted vision to the left. On examination, she had a mild left braciofacial hemiparesis with brisker tendon reflexes on the left and slightly increased motor tone, severe visual and somatosensory hemineglect and a partial left homonymous hemianopia. There was mild hypaesthesia in the left arm, a complete loss of JPS sense in the fingers and astereognosis on the left. She had severe clumsiness of the left hand, postural instability and disturbed force control. In addition she had bilateral mild constructional apraxia, asomatognosia for the left arm and mild dressing apraxia. She often misreached with the left arm. Under intensive physiotherapy she improved only slowly. CT scans demonstrated a right parieto-occipital infarction and a small hypodense area on the left side. Doppler sonography showed an occlusion of the right internal carotid artery.

Case 7

G.H., female, aged 57 yrs, right-handed. This patient had had several minor strokes within the last 14 years due to embolism from a mitral valve prosthesis. She was put on anticoagulants. One day before admission she developed a right occipital intracerebral haemorrhage which caused a left homonymous hemianopia. On examination, apart from the hemianopia, visuomotor ataxia for the left hand and neglect to the left were found. There was complete astereognosis in the left hand, whereas cutaneous sensation was normal. There was no weakness of the left arm or hand, motor tone was normal, and the tendon reflexes were symmetric. Reaching was only marginally disturbed. A mild expressive aphasia with mild acalculia and right-left disorientation were the only residual signs from her former strokes. Hand function on the right was normal. CT scans demonstrated a right occipitoparietal infarct and an old small left parietal and angular gyrus infarct.

Case 8

M.R., female, aged 40 yrs, right-handed. Three weeks before admission she had noticed persisting numbness of the right hand with difficulty in performing fine movements. Two weeks later an amnestic aphasia with impaired word finding and agraphia and alexia developed slowly. She showed a mild hemiparesis with normal motor tone but increased tendon reflexes of the right, mild cutaneous somatosensory deficits, complete astereognosis, and a right homonymous hemianopia. Agraphia, right-left disorientation, acalculia and alexia were the neuropsychological deficits. Although fine movements with the right hand were slow and clumsy, she could catch a ball and reaching was normal. CT scans showed infarction in the left posterior parietal lobe. Angiography showed a stenosis of the middle cerebral artery.

Case 9

P.F., male, aged 58 yrs, left-handed. Two months before admission he had noticed numbness and weakness of the left hand and 1 month later, mild weakness of the left leg. On admission, the most obvious finding was clumsiness of the left hand with mild weakness. Muscle tone was normal; the tendon reflexes were increased on the left. There was no hypaesthesia, but JPS in the left hand was mildly and stereognosis severely disturbed. VS was normal. Prehension and fine manipulation with the left hand was clumsy and slow, and showed postural instability and disturbed force control. Target-directed reaching was impaired, so that he also misreached under visual guidance. There was visual and somatosensory neglect to the left. CT and MRI scans showed 3 hypodense lesions in the territory of the right middle cerebral artery, 1 of them in the superior parietal region, the others in the centrum semiovale and deep to the precentral sulcus. The latter lesion was located medially near the interhemispheric fissure and was interpreted as being responsible for the weakness of the left leg. Angiography and laboratory findings led to the diagnosis of intracranial vasculitis. The 2 small subcortical lesions are not shown on the surface view in fig. 1.

Classification of lesion site

According to the site of the lesions in relation to the central sulcus, we defined three groups of patients. Cases 1 and 2 had lesions on CT scans immediately bordering the central sulcus at its posterior bank. They were classified as *anterior parietal*. Cases 3–6 showed lesions that were located in the postcentral gyrus, but extending into the posterior parietal cortex. They were classified as *combined parietal lesions*.

Cases 7–9 had lesions of posterior parietal cortex that did not extend into the postcentral gyrus. They were classified as *posterior parietal lesions*.

RESULTS

The nature of the sensorimotor deficits

The consistent features of the parietal motor deficits that have been observed in spite of the heterogeneity of the lesions, with frequent involvement of pyramidal function, will be described in this section. Testing of motor performance was divided into tasks measuring force and position control, and tests of exploratory and skilled finger movements. Each task was first performed with the hand contralateral to the lesion and then with the ipsilateral hand. The typical deficits were also monitored on video tape. The only patient with a bilateral parietal lesion (Case 7) had no abnormalities in any aspect of hand function tested on the right side.

Paresis

Most patients had an initial paresis of the limbs contralateral to the lesion, resolving almost completely. As described in the Case Reports, 2 patients had lesions extending into the precentral gyrus, but had only mild concomitant persisting weakness. The patients' history provided evidence that, in most cases, there was initial transient pyramidal dysfunction during the oedema phase of the infarcts. Maximal grip force is a suitable estimator of residual weakness due to pyramidal damage because it is not reduced in pure parietal motor disturbances. Grip force was examined for all patients with a rubber ball connected to a manometer.

Fig. 2 compares the dynamometer measurements for the affected and unaffected hands. The mean dynamometer values for the affected and unaffected hands showed a mean difference of 20 kPa. An age-matched control group showed a mean difference of 10 kPa between the preferred and nonpreferred hands. Despite the fact that both with the Wilcoxon test ($T = 4$) and the t test ($t = 8.7$; $P < 0.05$) the difference was significant, grip strength was always sufficient to hold and manipulate even heavier objects.

Disturbance of force and position control

The inability to maintain a constant posture of the fingers, hand and arm when the patient was asked to keep the arms outstretched and the fingers spread while the eyes were closed (postural instability) with the assumption of dystonic postures, athetoid movements of the fingers and pseudoathetotic wandering were observed in 6 patients (Cases 1–4, 6, 9). The affected arm was usually elevated and slightly supinated and the phalanges overextended.

The ability to maintain a constant given force level was measured by a strain gauge fixed to the index finger. Force was displayed on an oscilloscope together with a second trace indicating target force. In the hold task the patient had to maintain a force level adjusted to 30% of maximal force. After 8 s the oscilloscope blanked and the patient

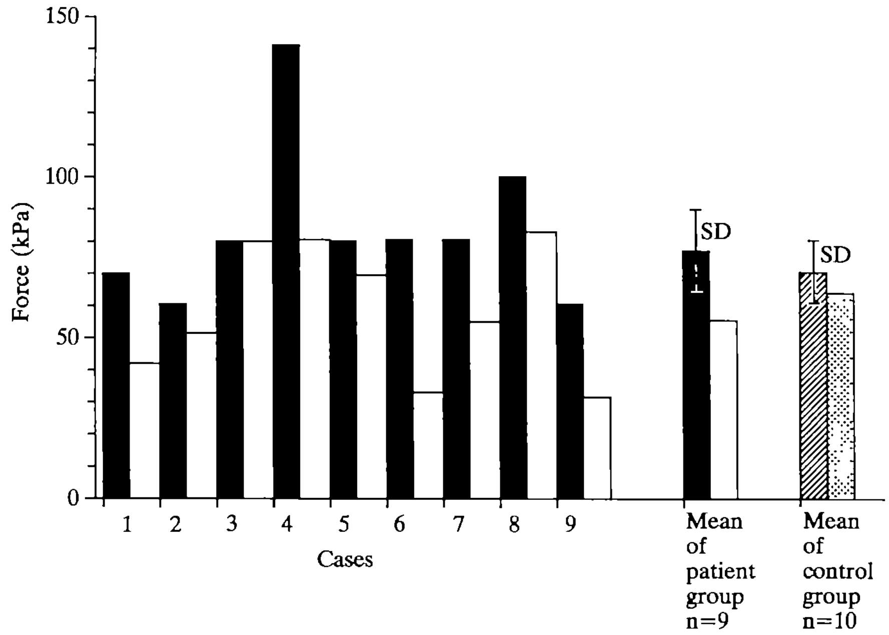

FIG. 2. Comparison of maximal grip force (mean values of 3 trials) ipsi and contralateral to the side of the lesion shown for each patient. On the right, population means and SDs are given for the patient group and age-matched controls. Open bars = affected hand; closed bars = unaffected hand; hatched bar = preferred hand; speckled bar = nonpreferred hand.

had to maintain the force level steady for a further 16 s. After 5 successive trials the average force level was compared for the 2 consecutive time segments. Before each test run the patient had 5 trials for practice. This task was poorly performed by those patients who also showed postural instability, so that the final force deviated by more than 50% from the target force soon after blanking in 5 successive trials.

Tapping

The measurement of tapping rate was performed with a special stylus. This and the subsequent tests are subtests of the Tübinger Motorische Leistungsserie (Hamster, 1980), a modified version of the Purdue Pegboard Test. Each contact of the tip of the stylus with a metal plate was measured. A score was obtained by tapping as fast as possible for 32 s. The number of contacts for the first 16 s and the second 16 s were counted electronically and their average tapping rate was calculated.

This test of fast repetitive movements was compared with standard values obtained for a normal population. Eight of the 9 patients were tested. As shown in fig. 3, the mean values of the unaffected hands were 5–6 taps/s, which was within the 20% range of the normal population. All parietal patients scored less well with the affected hand, but larger side differences were found only in 4 patients. Statistical analysis for 'tapping' showed with the Wilcoxon test and the t test ($t = 2.64$; $P < 0.05$) a significant difference,

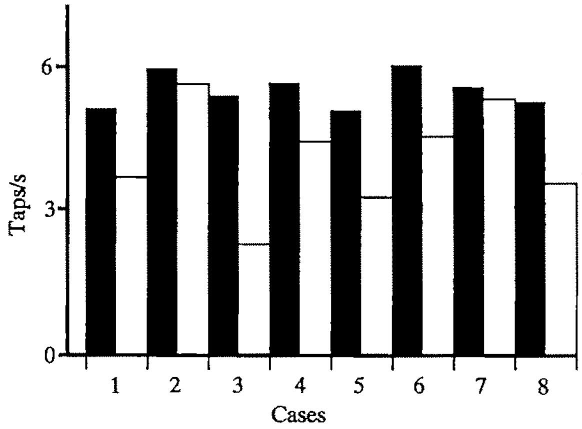

FIG. 3. Comparison of fastest tapping rates with the affected and the nonaffected hand (mean rates during 32 s) in 8 patients. The 25% percentile of the normal population was at 6/s. Symbols as in fig. 1.

but again, as with hand grip strength, the differences were small. Those patients having a more pronounced force deficit (Cases 4, 6, 9) also demonstrated the largest tapping difference.

Visuomotor performance

The usual clinical tests of pointing movements (finger-to-nose, finger-to-finger with and without vision), as well as reaching and grasping movements, were examined for each patient. All patients were tested at catching a tennis ball with the affected hand. Two patients (Cases 3, 6) showed clear visuomotor ataxia. Both showed gross misreaching only with the affected hand but in both hemifields (crossed and uncrossed visuomotor ataxia according to Rondot *et al.*, 1977). Grasping the ball when catching was characterized by slow and delayed finger flexion with inadequate formation of the hand aperture. The transportation phase was also deranged and misdirected from the outset. These visuomotor disturbances correspond to those described in detail by Jeannerod and Prablanc (1983).

For quantitative testing we used the aiming test, a standardized visuomotor control test from the Tübinger Motorische Leistungsserie. A score is obtained by attempting to hit 20 flat metal circles (diameter 6 mm, distance 12 mm) ordered in a row as fast as possible with a pin of 2 mm diameter. The time from contact with the first to contact with the last target area was measured electronically, as well as the number of misses. Eight out of 9 patients were tested. With the unaffected hand they scored a mean value of 12.4 s, ranging from 6.5 to 15.9 s. With the hand contralateral to the lesion the mean value was 23.1 s. This is very slow and is well under the 0.1% range (16.6–18.9 s) of the normal population. For most of the patients this task was very difficult and required much effort, but all succeeded in finishing the performance.

The 2 patients with visuomotor ataxia usually failed to grasp a target at the first attempt.

When they noticed the failure, they started to correct the position of the hand under visual control and finally grasped the object successfully. All reaching movements of these patients, especially their correction movements, were obviously slow. One patient had assumed a strategy with long target fixation and rapid but inaccurate reaching movements. In those patients without clinical evidence of misreaching, quantitative analysis (*see* fig. 4) revealed disturbances of the temporal aspect of the transport and landing phases. As depicted in fig. 4, reaching a small glass bowl is performed with the unaffected hand within 1 – 1.4 s. The trajectories show a smooth transition of vertical and horizontal movement components and a few corrections of the aperture between thumb and index finger during the landing phase. With the affected hand the movement lasts about 6 s and the transport phase shows a separation of vertical and horizontal movement components. The time taken for the transport phase is about 1.5 s. The landing phase is extremely slow (duration about 4 s) and shows repeated corrections of the aperture.

Manipulation

The patient had to transpose 25 pins of 2 mm diameter and 50 mm length from one row of 20 cm length on the metal test board of the Tübinger Motorische Leistungsserie into a second row of holes 30 mm apart. This task is a test for grasping, aiming and

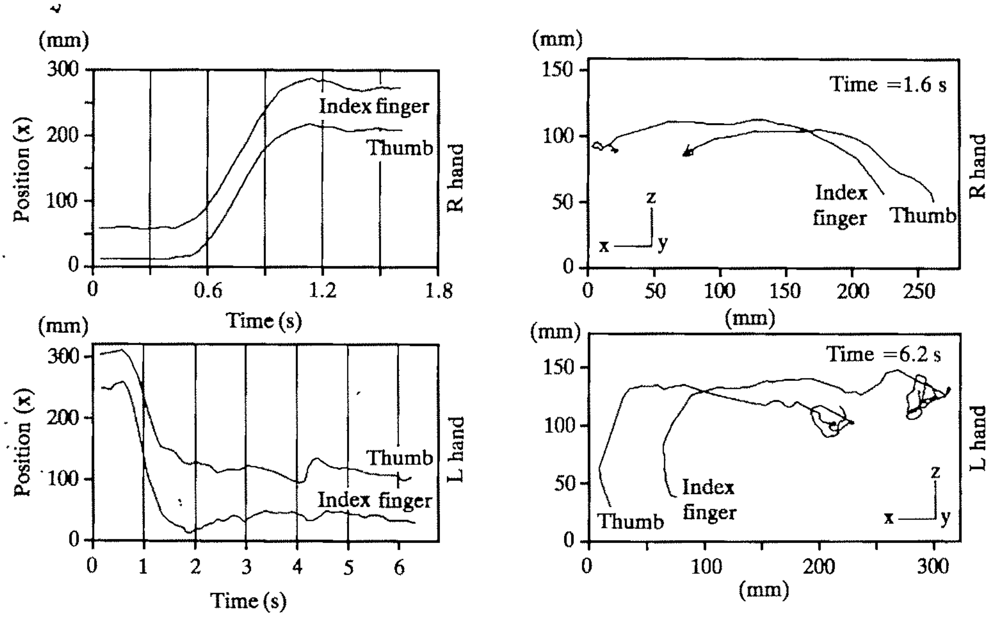

FIG. 4. Trajectories of a reaching and grasping movement (*right side*) of the unaffected right and the affected left hand (*Case 3*). The task was to grasp a small glass bowl placed 25 cm away from and 5 cm above the starting position of the hand. The recordings show the trajectories from the first movement of the hand until the first movement of the bowl. The starting position is indicated by 'thumb' and 'index finger', so that each hand approaches the target from the opposite position. The *left side* demonstrates the temporal course of the movements in the x direction. Transport and landing phases are both essentially slower with the affected hand (note different time scales!).

releasing. The essential parameter is the time spent for the whole performance. Cases 3, 4 and 6 found it impossible to perform this test within a reasonable time limit with the affected hand. All other patients also scored very poorly with their affected hand (93.9 s) as compared with the 50% value of the normal population (39.0 s). We consistently observed that the grasping component was the most difficult part of this test. The pins were frequently lost during retrieval from the holes.

Pincer grip

Under visual control the patient has to grasp a toy marble (diameter 12.4 mm) lying in a hole exactly adjusted to the diameter of the marble with a depth of half its diameter, then lift it and put it into a box; 5 s were given for each of 10 trials starting from a position of the hand 10 cm distant from the marbles. The successful trials were counted. This task was flawlessly performed with the unaffected hand by all patients. It was a difficult task because the force of the pincer grip had to be adjusted exactly to a level at which the friction was sufficient to lift the marble. If the force level was too high the marble was pressed into the hole instead of lifted, if it was too low the fingers slid over the marble. Additionally, there is an optimal posture of the fingers for success of this task. When testing this paradigm it was remarkable that all patients had a similar, more or less pronounced dystonic posture of the affected hand with overextended phalanges. The performances were quite different: while patients with severe simple sensory deficits but more anteriorly located lesions (Cases 1, 2) scored surprisingly well (7 successful trials out of 10), all patients with more posteriorly located lesions scored less well, despite better sensibility. Two of them (Cases 3, 4) did not have a single successful trial.

Exploratory movements

Tactile exploration of small objects with the hand is not performed in a stereotyped manner by different normal individuals. There are, however, some common features. These are rolling and supporting movements of the fingers III–V, bringing the object into a position between the index finger and thumb, and alternating exploratory movements followed by static enclosing movements. None of the patients had normal exploratory movements with the affected hand. The most severely disturbed exploratory pattern was characterized by a stereotyped closing and opening of the fist with squeezing of the object (which was laid on the palm of the hand) without using the thumb and the index fingertip for object contact. There was some, but no consistent correlation between the quality of the exploratory movements and the success of tactile recognition. Case 1 had only a slightly reduced movement repertoire but was unable to recognize even 1 of the 20 test objects.

For scoring the relative disturbance of the tactile exploration of objects, motor performance with the hand was classified after repeated display on the video tape. Ten different aspects of the movements during object exploration were scored (in ascending order of level of performance). (1) Visible movement without any relation to the object.

(2) Object-related movements without grasping. (3) Continuous object contact during exploration but no purposive prehension. (4) Performance of roll movements of the object but without individual finger movements. (5) Individual finger movements during manipulation, but no thumb opposition. (6) Performance of opposition of the thumb (forming a pincer grip position) but disordered alternating movements. (7) Adequate alternating movements of thumb and index finger. (8) Fluent movement pattern of all moving parts, but deranged scan paths of thumb and index finger. (9) Adequate scan path of thumb and index fingertip but inadequate force level. As the latter could not be measured, it was estimated on the basis of repeated analysis of video recordings. Criterion for this score was the inadequacy of object handling in spite of normal finger movement patterns. Loss of objects during exploration was one consequence of disturbed force control. (10) Normal movements, that is, as in (9), but with adequate force adjustment. If during the exploration of the 20 objects the above-mentioned movement characteristics were observed consistently, the patients could score maximally 10 points (1 point for each class).

Comparison between sensory deficits and motor performance

The relation between the sensory deficits and motor performance was displayed by sensory-motor profiles comparing the affected with the unaffected hand. Three of them illustrating different combinations of deficits are shown in fig. 5. Case 1 with a well demarcated lesion of the postcentral gyrus demonstrated a total loss of sensibility and tactile recognition in the left hand, which was virtually identical to the deficits in patients with complete deafferentation. She did not score a single point on sensory testing. The motor deficit was surprisingly mild in spite of a moderate additional paresis. Position and force control testing yielded mild deficits. Testing of exploratory and skilled movements disclosed a poor performance of the pin manipulation task, but she was successful with the pincer grip and surprisingly even with exploratory movements. She must have been able to generate a spatial object-like movement concept, despite the lack of sensory information, and to recall the exploratory movement patterns which of course were never performed in an adequate relation to the explored object. Concerning the pincer grip which was also successfully performed with the affected hand, she could control, almost perfectly, hand posturing under visual control.

Case 4 had a lesion comprising part of the postcentral gyrus and additionally of the posterior parietal cortex. Sensory testing revealed a moderate to severe deficit. Tactile recognition was severely disturbed. On the motor side, he had almost no paresis but scored very poorly for tapping and aiming and was almost unable to perform useful skilled and exploratory movements.

The third profile is drawn from Case 8 with a small lesion within the posterior parietal cortex. She had a mild to moderate somatosensory disturbance, only two-point discrimination being severely reduced, but she had extreme difficulty with tactile recognition for all tested paradigms. She scored within the normal range for all position and force control tests but had moderate to severe deficits with skilled and exploratory movements.

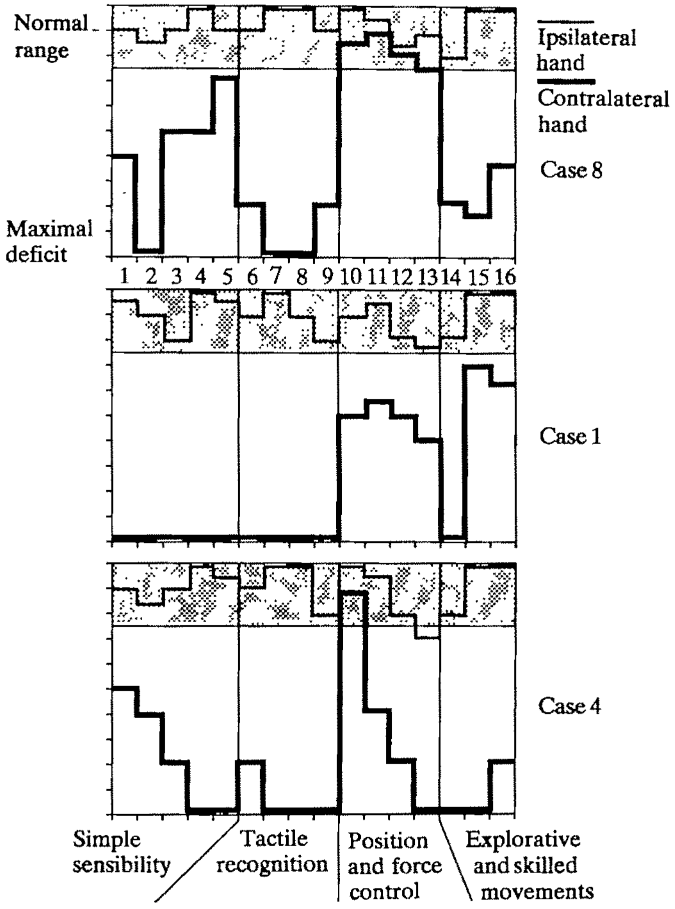

FIG. 5. Individual profiles of sensory and motor performance shown for both hands of *Cases 1, 4, 8.* The scores (ordinate) were arranged between normal and maximal deficit for four task groups. Two of these referred to somatosensory function; simple somaesthesis (1–5 on abscissa) and tactile recognition (6–9) and two to motor capacities: position/force control (10–13) and exploratory movements (14–16).

Index of measurement units: 1 = light touch (0/10–10/10 perception of the number of touches by a 1 g von Frey hair at the finger tip); 2 = two-point discrimination at the finger tip (0–20 mm); 3 = successive two-point discrimination at the palm (0–50 mm); 4 = vibration (128 Hz; 0/8–8/8); 5 = position sense of third phalanx of index finger (0–20 mm); 6 = texture recognition (number of surface textures recognized; 0–10); 7 = form discrimination (number of objects recognized; 0–10); 8 = visuotactile matching (number of cubes of different shape that were shown on a TV screen in front of the patient and correctly recognized tactually, 0–10); 9 = number of relief figures recognized (0–10); 10 = grip force (0–1.0 bar); 11 = maintenance of force level after feed-back blanking (percentage deviation 0–100); 12 = tapping (mean rate measured over 32 s, 0–6/s); 13 = aiming (time for task completion 5–25 s); 14 = manipulation (time to change 20 pins, 100–200 s); 15 = pincer grip (number of successful trials 0–10); 16 = exploratory movements scored according to the criteria given in the text (0–10).

These different profiles illustrate that a complete sensory deficit as in deafferented patients is not necessarily associated with motor deficits as severe as in patients with posterior parietal lesions. They further illustrate that a dissociation of simple somatosensory deficits and complex somatosensory function may be associated with a dissociation of reasonable force and position control, and the poor performance of skilled manipulation and object exploration.

Fig. 6 shows data obtained from the affected hands of all patients. Mean values of each task group were shown for all patients with lesions in anterior or posterior parts of the parietal lobe or with lesions involving both parts. The following results emerge from this figure. (1) In patients with anterior lesions the simple somatosensory and motor functions were disturbed to about an equal extent as the complex functions. (2) In patients with lesions involving the posterior parietal cortex, complex somatosensory and motor functions were clearly more disturbed than the simple ones. (3) Three out of 4 patients with combined lesions showed severe deficits of complex sensory and motor function whereas simple somatosensory were less and motor functions were least disturbed.

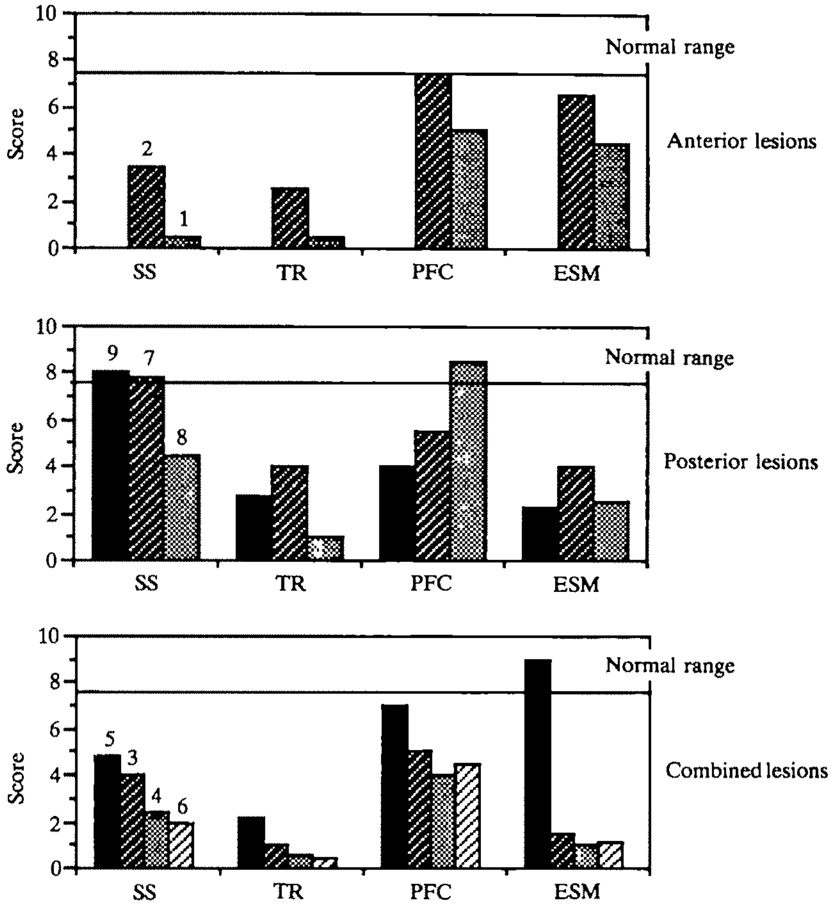

FIG. 6. Profiles of sensory and motor performance shown for the affected hands of all patients. Same score ordinate as used in fig. 5. The mean score calculated for each patient and each task group (SS, TR, PFC, ESM) is represented by one column. The left column in each row indicates the case number. SS = simple somatosensory; TR = tactile recognition; PFC = position force control; EMS = exploratory and skilled movements.

Measurements of finger trajectories during tactile exploration

In 4 patients finger movements were recorded by means of an optoelectronic system. The movement trajectories of the scanning thumb and forefinger during a 6 s epoch of tactile exploration without visual control of a ball are shown in fig. 7. The task was to discover whether the ball had a small elevation or not. The recording from the unaffected left hand of Case 8 is shown on the upper left side, and from the affected right hand on the upper right side. This patient had a lesion of the left posterior parietal cortex and a severe disturbance of exploratory hand and finger movements. The recording shows the movements of the thumb and forefinger in x and y directions viewing the finger tips from the front. The recording from the unaffected hand illustrates the typical normal scan path formation. The affected hand reveals paucity of movement and a deranged trajectory formation that is distinctly different from the normal movement pattern.

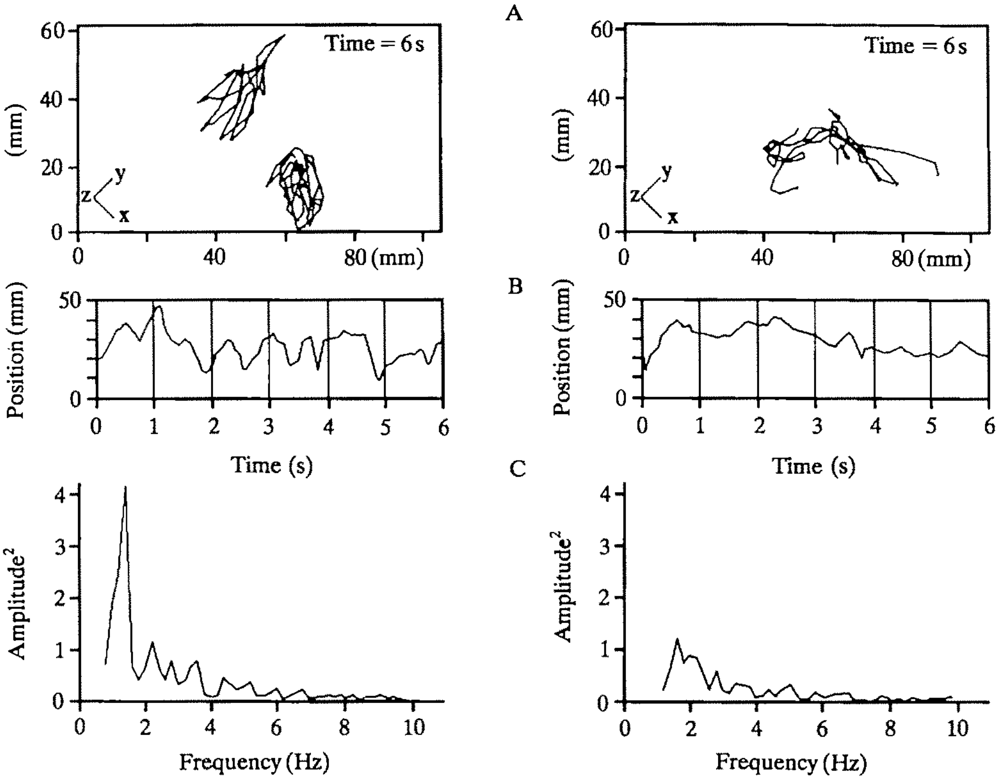

FIG. 7. Spatial and temporal characteristics of exploratory finger movements during tactile exploration of a ball as revealed by an optoelectronic system. In A, the movement trajectories of the forefinger and thumb are shown as viewed from the front, so that the vertical and horizontal movement components are displayed. The *left side* shows the performance of the unaffected and the *right side* of the affected hand of *Case 8*. The workspace of the scanning movements is smaller and more irregular for the affected hand, and fingers are closer together because the patient had already lost the ball without noticing it. In B, the temporal profile of the vertical movement trajectories is shown on the *left side* for the unaffected and on the *right* for the affected hand. The corresponding power spectra (C) show that the normal regular sinusoidal movement, as reflected by a prominent peak, is decomposed for the affected hand.

The temporal characteristics of these digital movements are also profoundly altered. Fig. 7B illustrates the position of the unaffected forefinger (left) in the vertical direction plotted over time. The dynamic digital palpation of an object for the sampling of shape information with the unaffected hand consists of periods of fairly regular sinusoidal movements of the fingerpad across the object. Such periods are usually interposed between short times of static encompassings. Each half sinusoid represents the movement of the finger along one digital scan path. Spectral analysis of a 6 s epoch of normal object exploration reveals the prominent sinusoidal movement component represented by a sharp peak at about 1 Hz (fig. 7C). The recording from the affected hand on the lower right shows the destruction of this sequential sampling process that normally provides the basis of tactile recognition.

When the velocity profile along one scan path is plotted (fig. 8), a typical bell-shaped profile is obtained for the normal forefinger movement (*see* fig. 8A), so that velocity is low close to both ends of the path and high in the middle. On the affected side (fig. 8B) velocity is much lower and varies randomly along the path.

This disturbance could indicate that the capacity of the hand or fingers to perform any type of rhythmic serial movements is lost. Fig. 9 shows that this is not the case. When the same patient is asked to tap with the affected hand (left) as fast as possible, he can do this surprisingly well (lower graph). Repetitive tapping movements between forefinger and thumb are less regular (upper graph) but the characteristic movement pattern can still be recognized.

This selective disturbance of particular sensorimotor interactions is further illustrated in fig. 10. Case 4 was first asked to recognize an object which was laid in his palm. He hardly performed any finger movements (upper part of fig. 10) but, when asked to imitate with the affected hand the finger movements that were shown to him, there was a striking difference between the imitation and tactile exploration. We therefore conclude from our recordings that, in contrast to pyramidal damage, it is not any motor

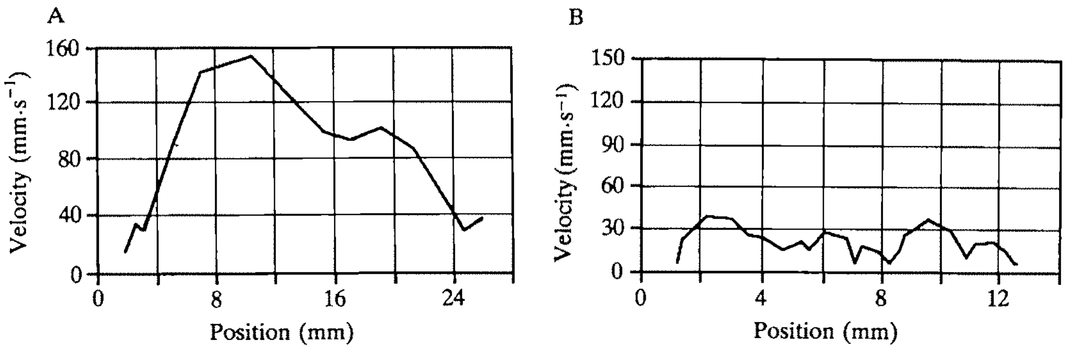

FIG. 8. The velocity profile along a single scan path of the forefinger pad across the surface of a cube is shown in A for the unaffected hand of the same patient as shown in fig. 7, and in B for the affected hand. The length of the path is about 24 mm for the unaffected and 11 mm for the affected hand. Peak velocity for the unaffected hand is about 150 mm·s^{-1}, but only below 40 mm·s^{-1} for the affected hand, where it is irregular along the whole scan path.

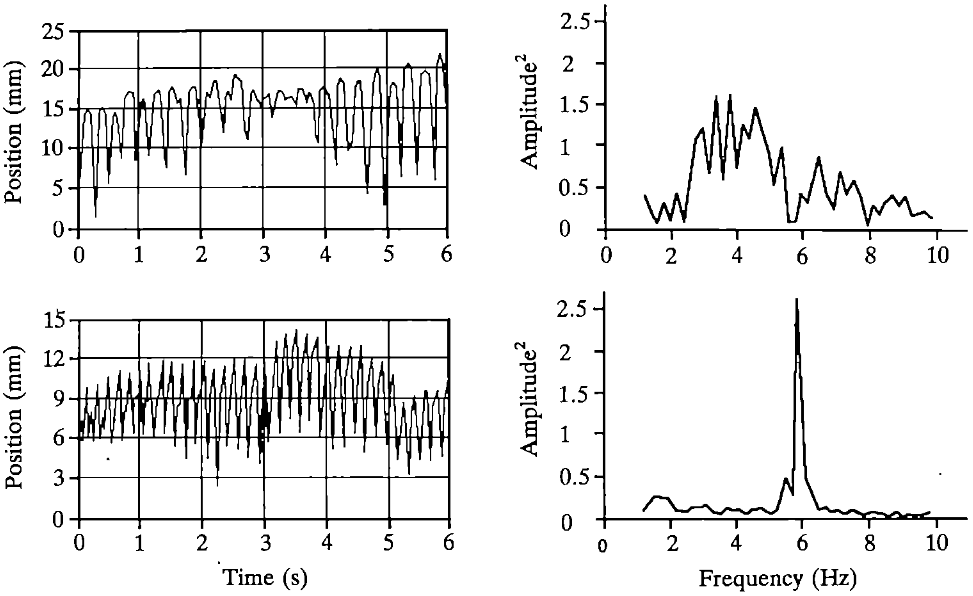

FIG. 9. The *lower part* shows the temporal profile of the forefinger movements when *Case 8*, whose recordings are shown in figs 7 and 8, was asked to tap with his affected hand as fast as possible. The *upper part* shows the vertical forefinger movement when asked to tap with his forefinger against the thumb as fast as possible. Whereas hand tapping was equally fast and regular as in normal subjects, finger tapping was slower and less regular than hand tapping, which appears most clearly in the power spectra alongside the corresponding profiles.

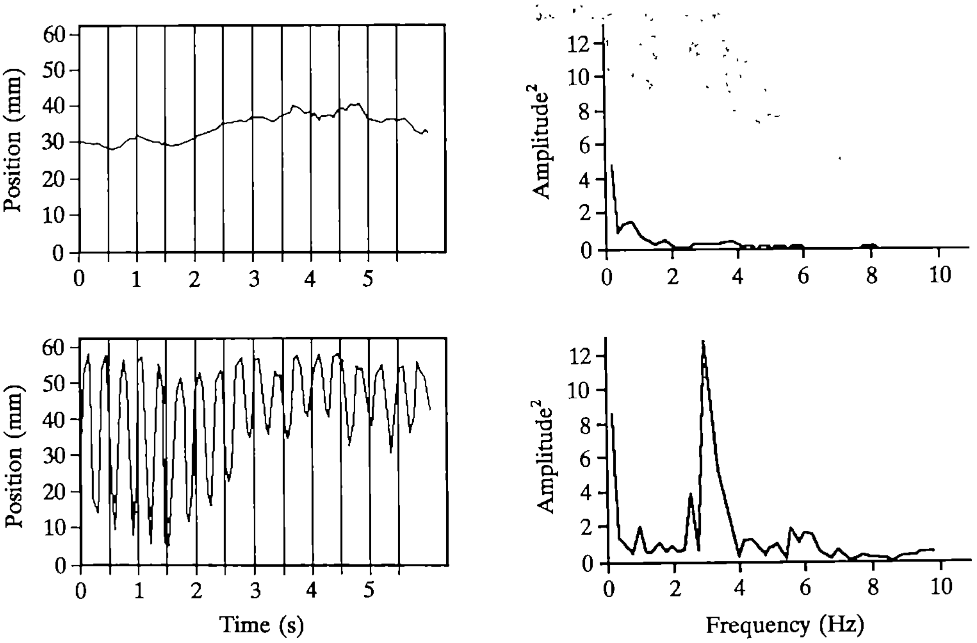

FIG. 10. Temporal profile of the vertical forefinger movement during tactile exploration with the affected hand of *Case 4*. In the trial depicted the patient does not perform any apparent movement when an object is put in his palm and he is asked to explore it (*upper part*). When typical exploratory finger movements were shown to him and he was asked to imitate them, he performed as demonstrated in the *lower part*.

act requiring individual finger movements that is disturbed, but its evocation by sensory stimuli.

The same phenomena which are depicted for Cases 4 and 8 could also be seen on the recordings of Case 7, while Case 1, despite her severe sensory deficits, could perform almost normal scanning movements; however, obviously only memorizing the objects which often had fallen out of her hand without her noticing, while she continued the 'explorative' movements.

DISCUSSION

The relationship between somatosensory and motor deficits

The analysis of the somatosensory deficits in the patients described in this article was not primarily performed in order to evaluate sensory function, but rather to provide a basis for the comparison with the motor deficits. Following Mountcastle's (1984) definition, we refer to the appreciation of contact, of stimulus movement and the crude localization of stimuli as the simple aspects of somaesthesis, and to the appreciation of the temporally changing and spatially distributed properties of mechanical cutaneous stimuli as complex aspects. Correspondingly, the simple motor functions of force and position control were compared with the complex explorative and manipulative finger movements.

The lesions were subdivided into three categories on the basis of their distribution within the parietal lobe. Two patients had lesions restricted to the anterior part. In 3 patients the damaged areas lay behind the postcentral gyrus in the posterior parietal region. Four patients had combined lesions involving both parts. Although such a small sample size does not allow a thorough statistical analysis, the data elaborated for these rare cases with such restricted lesions reveal some new information about the relationship between somatosensory and motor function in human patients.

The major problem of any correlation between neurological deficits and the location and extent of lesions as revealed by organ-imaging techniques is the difficulty in estimating the functional implications of structural alterations. There is clear evidence that regional abnormalities as shown by CT or MRI scans can be associated with the preservation of normal function in the affected area, but also with total loss (Freund, 1987*a*). CT scan numbers on the Hounsfield scale below +10 are usually associated with loss of function in that area. Our cases all had chronic well-circumscribed lesions with hypodensities in that range. The proof of the functional significance of these lesions came from the tests on sensorimotor performance which showed pathological results for the hand contralateral to the lesions in all cases. Comparison of the single case data shown in fig. 6 reveals that the nature of the sensorimotor dysfunction was different in the patients with anterior and posterior parietal damage.

With respect to somaesthesis, simple and complex somatosensory functions were about equally severely disturbed in patients with more anteriorly located lesions, whereas complex somaesthesis was preferentially disturbed in patients with posterior parietal damage. Force and position control representing the simple motor functions were relatively well preserved in all cases, whereas complex explorative and manipulative finger movements were preferentially disturbed in the cases with lesions of the posterior parietal cortex. In patients with anterior parietal lesions these movements were surprisingly well preserved, although the lesions were closer to the precentral gyrus. Some of these patients also had initial pyramidal signs, but nevertheless regained the motor capacities of the hand and fingers better than those with lesions more remote from the primary motor cortex. As shown in fig. 6, patients with posterior or combined parietal lesions showed a similar severity for the disturbance of the complex somatosensory and complex motor functions. The most pronounced complex motor deficits were seen in patients with combined lesions involving anterior and posterior parts of the parietal cortex, followed by patients with damage of the posterior parietal cortex. Case 2 and, in particular, Case 1, show (fig. 6) how well motor functions can be preserved even in a patient who is almost fully deafferented. These 2 patients show further that complex motor functions can remain surprisingly good when complex somaesthesis is severely disturbed.

It is thus not possible to conclude that the severity of the motor deficits in parietal lobe disease is simply proportional to the degree of somatosensory disturbance. Interestingly, this was the case in all our patients with posterior and combined lesions, but not in the 2 anterior cases. The conclusion that posterior parietal cortex is relevant for the elaboration of motor commands required for explorative and manipulative hand movements is supported by the optoelectronic recordings that were performed on 4 patients (Cases, 1, 4, 7, 8). They showed the loss of adequate manipulative finger movements although Cases 7 and 8 could feel the object in their hand. In the traditional sense this is an apraxia, because performance of the movement is not totally impossible; it can only be achieved under certain circumstances. This tactile apraxia corresponds to Geschwind's (1965) conception of the apraxias as disturbed sensorimotor interactions. In that sense, the definition of the stimulus-response relationship is of critical importance for the definition of a given apraxia. In our cases, the specificity of the stimulus-response relation was shown for 2 patients with posterior parietal damage, where optoelectronic recordings revealed the destruction of the spatial and temporal characteristics of digital object exploration.

These recordings (fig. 10) further demonstrated that these movement patterns are not lost. They can be generated on imitation, but not for exploration. Therefore they are functionally irrelevant for the patients: they are not automatically elicited by the usual somatosensory input, that is, by the adequate behavioural context. Although the ability to perform this type of movement is basically preserved, they are functionally useless, because execution is only possible in the inappropriate context. Our present inability to understand sensorimotor interaction better is illustrated by the fact that these patients do not benefit from the preservation of the gestural pattern of exploration, because it can obviously not be triggered by and related to the object. Surprisingly, this was possible to some extent in Case 1 who was quasideafferented. Although she also could not match the movement trajectories to the object and was not aware when losing the object, these movements looked purposive even by inspection and resembled an explorative movement.

Our only explanation for this paradoxical result was that she knew that she was supposed to explore an object and in spite of the lack of sensation generated the stereotyped explorative gestures trying to match them to the remembered object shape.

Our results are in accordance with observations made by Roland and Mortensen (1987) who described 10 patients with parietal lesions and discrimination loss but preserved object manipulation. What we have not observed at all in parietal lobe damage is the preservation of tactile recognition in cases with severely disturbed exploratory movements.

The role of visual guidance for the compensation of disturbed hand function was also different for the patients with anterior and posterior parietal lesions. In the former cases with preferential impairment of simple somaesthesis, vision was an effective compensatory mechanism. In contrast, the severe impairment of complex motor functions usually associated with complex somatosensory deficits showed little benefit from visual control and never allowed adequate manipulation.

A preferential impairment of sensorimotor deficits was not observed in patients with missile wounds in the posterior parietal area by Semmes *et al.* (1960). Injection of muscimol in the finger region of area 2 in monkeys led to complete yet reversible loss of finger coordination without weakness or disturbance of hand reach (Hikosaka *et al.*, 1985). In contrast, Stein (1978) concluded from his cooling experiments in the parietal cortex that Brodmann area 5 is concerned with controlling contralateral movements in relation to cutaneous and proprioceptive feedback, while area 7 is important for visuomotor control, a hypothesis proposed previously on the basis of single unit recordings from these areas (Mountcastle *et al.*, 1975; Hyvärinen, 1982; Seal *et al.*, 1982). Single unit studies showed further that posterior parietal cortex is relevant for the association of visual and somatosensory information with internal data (Robinson and Goldberg, 1978) and the representation of the position of the hand in two-dimensional space (Georgopoulos *et al.*, 1984).

These conclusions are in accordance with the clinical literature, where a disturbance of the body scheme, spatial agnosia, disturbances of topographical relationships, constructional apraxia, amorphosynthesis, visuomotor and tactuomotor disturbances have been frequently described in patients with lesions of the parieto-temporo-occipital region (Balint, 1909; Bender *et al.*, 1950; Denny-Brown and Banker, 1954; Hécaen *et al.*, 1956; Damasio and Benton, 1979; De Renzi *et al.*, 1983). Mesulam (1981) emphasized the role of posterior parietal cortex for providing an internal sensory map, whereas the limbic component in the cingulate gyrus regulates the spatial distribution of motivational valence. Such functions require the referencing of the external sensory maps with eye, head and body coordinates.

The role of afferent input for the entrainment and acquisition of skilled explorative and manipulative behaviour has been demonstrated by experiments on neonatal primates. They display reflex grasping to tactile stimulation of the palm that loses its stereotyped pattern during maturation. Monkeys that have experienced this process recover prehensile function after subsequent deafferentation, whereas monkeys deafferented in utero never develop prehension in spite of appropriate training (Taub *et al.*, 1966; Taub, 1980).

Experiments on the long-term effects of the unilateral removal of sensorimotor cortex in infant and adult rhesus monkeys showed that in spite of remarkable recovery for many basic motor acts, the independent use of thumb and forefinger was not possible in either the infant or the adult monkeys (Passingham *et al.*, 1983).

The examination of hand function in patients with parietal lobe damage discloses several aspects of disturbed sensorimotor interaction. The employment of the hand for whatever task requires a sequential motor performance starting with the reaching movement, the assumption of adequate hand posture during target acquisition, and then the execution of particular tasks, such as prehension and object exploration. All aspects of this composite movement were disturbed in our patients. Trajectory formation during reaching was clearly different between the affected and the nonaffected arm. Reaching was slower than normal, in particular close to the landing phase. Target acquisition was, however, appropriate, except in the 2 patients with visuomotor ataxia. The transport phase was thus altered, but much less than the subsequent formation of hand aperture, prehension and tactile exploration.

Lederman and Klatzky (1987) proposed that the haptic system engages a standard repertoire of exploratory procedures which represent stereotyped postural patterns having invariant characteristics. They found that certain exploratory procedures were typically linked with object-related properties. Pressure, static contact, unsupported holding and enclosure were some steady manual postures, whereas lateral motion and contour following were dynamic skills, which were specially engaged for object categories such as surface texture and contours. Object recognition depends on the assumption of adequate hand postures for different tasks and on dynamic digital scanning. Both are disturbed in patients with parietal lesions (Jeannerod *et al.*, 1984).

It is remarkable that these two aspects of active touch preserve their purposive action pattern in patients with lesions of precentral cortex, but only partial paresis. The motor dysfunctions in the cases with parietal lobe lesions are strikingly different from those described after lesions of the primary motor cortex. Freund (1987*a*) has reviewed some clinical observations on patients with lesions restricted to the precentral gyrus, and described 2 personal cases (1987*b*). In contrast to the parietal cases, patients with precentral lesions have paresis without significant increase of tone or reflexes. The essential deficit is deficient force generation and execution of independent finger movements. After partial recovery, the patients can control the residual force remarkably well. Once they regain the ability to maintain a certain force level, they can hold an egg between the fingers without squeezing or dropping it, even without visual control. The residual finger movements are clumsy and slow but purposive and appropriate to the object. This is also true for the formation of the hand aperture during grasping. As soon as the patient is able to bring his fingers in contact with an object to be explored, even if that is only possible by means of a flexion synergy of the fingers, he will be able to recognize simple objects. Such patients have no difficulties with stereognosis. This stands in striking contrast to patients with parietal lobe damage. In spite of ataxic movements and dysmetric force control with frequent coarse oscillations, their force range is almost normal. They have difficulties with hand activities requiring precise fine force control, and are much better at exerting stronger forces and performing coarse athletic motor acts.

Classifications of manipulative hand movements distinguished between power and precision grip (Napier, 1956) or gripping and handling (Landsmeer, 1962). Elliott and Connolly (1984) substituted a distinction between intrinsic and extrinsic hand movements for these former categories. Extrinsic hand movements were defined as movements of the hand or a prehended object as a whole and intrinsic movements as coordinated movements of the digits to manipulate an object within the hand. Kunesch *et al.* (1989) have found that such a distinction is not only based on behavioural and purposive criteria, but also reflects two different modes of sensorimotor interaction. Measurements of a broad range of natural manual activities showed that their temporal characteristics fell into two separate classes. The exploratory and manipulative finger movements representing intrinsic movements were consistently performed slowly with frequencies restricted to the 0.5–2 Hz range. In contrast, learned manual activities such as handwriting, pencil shading, erasing, and imitating extrinsic hand movements were performed much faster and lay in the 5–8 Hz range. There was no overlap between the frequency domains of these two types of movement.

Recordings from single mechanoreceptor nerve fibres from the fingerpad skin in the monkey have shown that the spatial characteristics of ridged surfaces that are moving across the fingerpad in passive touch experiments are encoded in the population response rather than in the discharge characteristics of individual mechanoreceptors (Darian-Smith and Oke, 1980). The optimal neural representation of the spatial dimensions of a geometric array of dots on a surface moving across the fingerpad skin requires tangential velocities of between 40 and 140 $\mathrm{mm \cdot s^{-1}}$ depending on the spatial frequencies of the dot pattern. Although innervation densities are different in the human fingerpad skin (Bolton *et al.*, 1966), these velocities correspond precisely to those measured for the moving finger in active touch experiments on human subjects (Roland and Mortensen, 1987; Kunesch *et al.*, 1989). This indicates that the temporal characteristics of these movements match the temporal requirements of the sensory input.

The complementation of clinical analysis of hand function by quantitative analysis that was performed in 4 patients revealed that the dynamics of digital palpation are disturbed in parietal lobe dysfunction. The breakdown of the finely tuned scanning process prevents the sequential sampling of mechanoreceptor information. The impairment of hand function in parietal lobe disease illustrates the intricate mutual dependence of the spatiotemporal organization of receptor activation by movement and of the formation of movement trajectories on the basis of adequate sensory processing.

There is cumulative evidence that several cortical areas within the posterior parietal cortex are involved in the processing of higher order aspects of motion perception and in the transformation of spatial coordinate frames into programmes for adequate motor behaviour (Andersen *et al.*, 1985; Siegel and Andersen, 1988). The segregation of information channels subserving different visual functions such as form, colour, depth and motion, is now firmly established (Ungerleider and Mishkin, 1982; Hubel and Livingstone, 1987). Different somaesthetic submodalities are also separately projected onto segregated subsets of cortical modules (Dykes *et al.*, 1982) and further processed in area 5.

Our data provide evidence that the segregation of submodality or feature-specific sensory input has its counterpart on the motor side, so that different sensorimotor task groups are processed along separate neuronal circuitries. The essence of the motor disturbance of the hand in parietal lobe disease lies in the disturbance of the conception and generation of the movement patterns necessary to bring those receptors into action which would normally provide the information required for the identification and manipulation of objects. This deficit is almost complementary to the preferentially proximal motor disturbance and normal performance of intrinsic hand movements in patients with lesions of premotor cortex (Freund and Hummelsheim, 1985). The parietal lobe is not only involved in the elaboration and further processing of somatosensory information, but also in the conception and generation of those motor programmes required to collect this information. This illustrates an important aspect of sensorimotor integration, the dependence of feature extraction on purposive action.

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INFLUENCE OF RESPONSE MODALITY ON PERCEPTUAL AWARENESS OF CONTRALESIONAL VISUAL STIMULI

by EDOARDO BISIACH, GIUSEPPE VALLAR *and* GIULIANO GEMINIANI

(*From the Institute of Clinical Neurology, University of Milan, Milan, Italy*)

SUMMARY

Visual extinction on double simultaneous stimulation was investigated in left and right brain-damaged patients in two response conditions: verbal and motor. In right brain-damaged patients contralesional detection was significantly worse when monitored by motor rather than by verbal responses in condition of single as well as of double stimulation. Previous research in normal subjects had shown that the left hemisphere is selectively involved in choice reactions such as those occurring in the motor condition of the present experiment in brain-damaged patients. The results of the latter are interpreted using as a basis the findings of that research and Kinsbourne's hemisphere activation hypothesis concerning unilateral neglect of space.

INTRODUCTION

One century after its discovery by Loeb in 1884 (Benton, 1956) and its subsequent introduction into clinical neurology by Oppenheim in 1885, contralesional extinction on double simultaneous stimulation remains a relatively simple phenomenon, the causation of which is still under discussion. This indeterminacy is a distinct challenge to cognitive neurobiology, since it exposes a discomforting lack of knowledge of basic neural mechanisms of perceptual awareness and of the dynamics of the stimulus-response interface. Uncertainty is added by the circumstance that it is still unclear whether the phenomenon lends itself to unitary explanation or not. A further complication is the possible left-right asymmetry of extinction in man which, although still in need of effective assessment, imposes definite constraints on the interpretation of the phenomenon.

The main (more or less explicit) opposing views in the literature are the 'sensory' and the 'attentional' types of explanation (*see*, e.g., Critchley, 1949). The former identifies the primary factor for extinction in the defective flow of information through the damaged hemisphere: the impaired message is held to be interfered with by concurrent information initially processed by the unlesioned hemisphere, or unable to compete with it. According to the latter view, the basic disorder should be sought at the level of mechanisms controlling lateral displacements of attention.

Quite expectedly, faulty responses to sensory stimulation may be found on the side contralateral to the brain lesion causing extinction, even with single-stimuli (Critchley, 1949, p. 547). However suggestive of a sensory origin for extinction, these findings

Correspondence to: Professor Edoardo Bisiach, Università di Milano, Istituto di Clinica Neurologica, Via Francesco Sforza 35, 20122 Milano, Italy.

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are no definite proof against competing interpretations; indeed, they might be associated with, although independent from, extinction, or in some instances they may themselves be manifestations of an attentional disorder (however this might be conceived). On the other hand, the concept of attention is so incompletely elucidated that an attempt to explain extinction using attention as a basis may easily lead to question-begging claims.

Relating extinction to unilateral neglect is a more definite move, the success of which, however, depends on how this syndrome is in its turn interpreted. If, following Denny-Brown *et al.* (1952), we subsume extinction under unilateral neglect but then proceed to explain the latter on a sensory basis, we encounter the same difficulties that confront sensory explanations directly applied to extinction itself (*see* below). If a different kind of explanation of unilateral neglect is offered, then a more articulated path is opened for an interpretation of extinction phenomena. This was the strategy adopted by Critchley (1949), who also explicitly related such phenomena to unilateral neglect. According to Critchley, extinction is due to a state of disadvantage for those stimuli brought to bear upon sensory areas which, as a consequence of the brain lesion, are less prominent within the patient's mental representation of his own body.

Nonsensory interpretations of unilateral neglect (Bisiach and Berti, 1987; Heilman *et al.*, 1987; Kinsbourne, 1987) can accommodate extinction phenomena. A nonsensory account of at least some such phenomena is necessitated by instances of visual extinction *within a single homonymous visual field.* In such instances, the simultaneous presentation of two horizontally separated stimuli in the unaffected half-field implies paradoxical extinction of the stimulus appearing on the *relatively* contralesional side, in spite of its greater proximity to the fovea. More formal evidence is provided by the remarkable study by Bellas *et al.* (1988). These authors observed contralesional olfactory extinction following unilateral brain lesions. As the olfactory pathways do not cross, a sensory explanation would have predicted ipsilesional extinction.

What remains to be established is (1) whether all instances of extinction appertain to the neglect syndrome, and (2) which variables influence extinction. The second point is particularly important: regardless of the ascription of extinction to a particular category of disorders, clarification of this point would contribute significantly to the understanding of the interactions of sensory processes in the brain and of their integration into cognitive activities.

The present paper reports the results of an investigation which was undertaken on the general assumption that at least a part of extinction phenomena pertains to unilateral neglect. Our specific aim was to test the hypothesis of Watson *et al.* (1978) that a possible determinant of neglect is directional hypokinesia, that is, a reluctance to initiate and maintain contralesionally directed activities, regardless of the side of the limb involved in those activities. We therefore asked our patients to signal their perceptual judgements with directional motor reactions, either leftward or rightward. A condition requiring verbal responses was also included for control purposes.

As will be related, we found partial, albeit significant, support for the directional hypokinesia hypothesis. An interesting dissociation in the detection of contralesional stimuli was, however, found in right brain-damaged subjects relative to the response modality (verbal vs motor). A tentative interpretation of this dissociation will be given in the Discussion.

MATERIAL AND METHODS

Subjects

Subjects were 14 left (LBD) and 32 right (RBD) brain-damaged patients with contralesional visual field defects ranging in severity from 1 to 3 on a standard bedside assessment based on a 'confrontation' technique and yielding scores on a 4-point scale ranging from 0 (no defect) to 3 (Bisiach *et al.*, 1986). They were selected from a continuous series of 199 right-handed adults suffering from unilateral brain damage (119 LBD and 80 RBD) without disordered vigilance, confusion, general mental deterioration or peripheral visual diseases. The presence of unilateral brain damage was diagnosed on the basis of clinical and, in most instances, radiological (CT scan) findings. Absence of homonymous visual field defects on the above-mentioned test had led to the exclusion of 52 LBD and 48 RBD patients; 53 LBD had to be excluded because of severe dysphasia, in whom it was of course impossible to determine how many had homonymous visual field defects. In the experimental groups, the pathology was vascular (13 LBD and 29 RBD) or neoplastic (1 LBD and 3 RBD). Of the LBD, 10 were males and 4 females, while in the RBD group 19 were males and 13 females. Ages ranged from 46 to 86 (mean 64 ± 13.40) yrs in the LBD and from 21 to 83 (mean: 63.78 ± 12.56) yrs in the RBD groups. Motor deficit, on a standard assessment yielding 3 as maximum score (Bisiach and Faglioni, 1974), ranged from 0 to 2 (mean: 0.36 ± 0.63) for the upper limb and from 0 to 3 (mean: 0.64 ± 1.08) for the lower limb in LBD, and from 0 to 3 (mean: 1.69 ± 1.28) for the upper limb and from 0 to 3 (mean: 1.69 ± 1.31) for the lower limb in RBD patients.

Stimuli and procedure

The front view of the apparatus used for the experiment is shown in fig. 1. The patient was seated at reaching distance from the front panel, the vertical midline of which lay on the sagittal midplane of his trunk and head. For each trial, following the examiner's order, the patient had to reach for the central button and press it with the forefinger of his *ipsilesional* hand. The size of the button required visual fixation during the reaching phase, so that the two halves of the front panel of the apparatus fell into the corresponding halves of the patient's visual field. Stimuli consisted of 200 ms flashes of red light emitted by the two diodes placed nearest to the upper left and right corners, respectively. On regular trials, pressing of the button was instantaneously followed either by a single left or right stimulus (S), i.e., by a flash from a single diode, or by a double stimulus (D), i.e., by a flash from both diodes. On catch trials no flashes were given.

There were two conditions, respectively, requiring verbal (V) and motor (M) responses. In condition V, which was run first, the patient had to report the number of the perceived stimuli verbally. Dysphasic patients unable to communicate verbally were allowed to use gestures. This condition consisted of a random

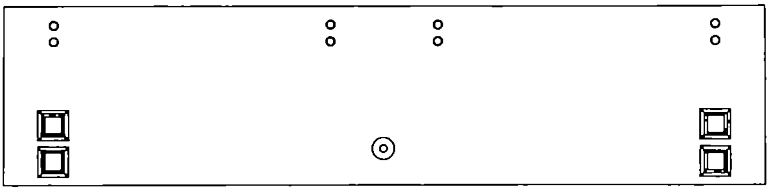

FIG. 1. Front view of the apparatus used in the experiment (reproduced from Bisiach *et al.*, 1985).

sequence of 40 trials: 10 left S, 10 right S, 10 D, and 10 catch trials. In condition M, pressing the button caused (in addition to the flashing of one, two, or no diodes) the immediate and persistent illumination of two red keys, one on the left and one on the right (bottom squares in fig. 1). Using the forefinger of his *ipsilesional* unaffected hand, the patient had to press one of the keys if he had perceived a single stimulus, whereas no response was due if two stimuli or none were perceived. Both response key lights went out when pressed by the patient or when the apparatus was reset by the experimenter for the next trial. Condition M consisted of four blocks of 20 trials each, ordered in an ABBA sequence, with preliminary instructions to press the key ipsilateral to the lesion in A and contralateral in B. The 20 trials of each block consisted of a random sequence of an equal number of left S, right S, D and catch trials.

D was chosen as the 'no-go' configuration for a two-fold reason. On the one hand, we wanted our patients to give a reasonably balanced number of positive and negative reactions throughout the motor condition of the experiment. Selecting S as 'no-go' input would have caused the number of positive reactions to fall to near zero in patients with a high extinction rate. On the other hand, this would have generated inadmissible ambiguity in the interpretation of negative reactions to contralesional single stimuli, that is, the impossibility of deciding whether such reactions indicated correct detection or failure.

RESULTS

In response to the original question, it was found that the detection of contralesional *single* stimuli in the RBD group was significantly better only when monitored by ipsilesionally, as opposed to contralesionally, directed motor reactions: the mean number of correct detections of left S (maximum possible score = 10) was, respectively, 3.66 ± 4.22 and 3.25 ± 4.02 (t for paired comparisons = 2.6273, df = 31, $P < 0.02$).

In order to compare our patients' performance in conditions V and M, the M scores were then collapsed, thus disregarding the lateral component of the motor reactions. Fig. 2 shows the percentage of correct responses given by LBD and RBD patients to contralesional stimuli in conditions V and M and in the conditions of single (white columns) and double stimulation (grey columns).

Since the patients' responses to ipsilesional single stimuli and on catch trials were errorless, the relative scores have been omitted.

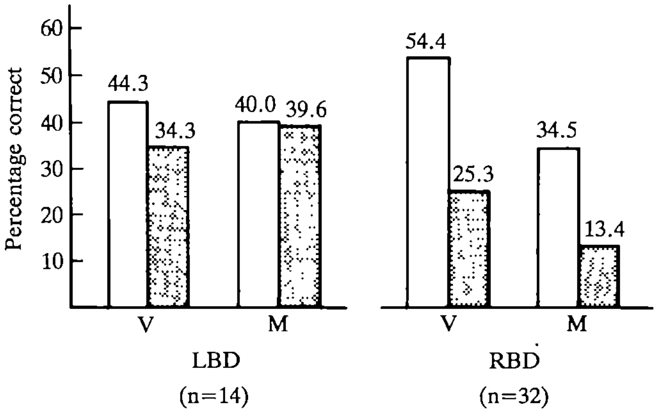

FIG. 2. Detection of contralesional stimuli by left (LBD) and right (RBD) brain-damaged patients in conditions of single (white columns) and double (grey columns) stimulation and of verbal (V) and motor (M) response.

A split-plot ANOVA (Kirk, 1968) with one between-subjects factor (group) and two within-subjects factors (stimulus and response) revealed significant main effects of stimulus (F = 12.980, df = 1, 44, $P < 0.001$) and response (F = 7.957, df = 1, 44, $P < 0.007$), but not of group (F = 0.416, df = 1, 44, n.s.). The group×stimulus interaction was significant (F = 5.614, df = 1, 44, $P < 0.021$), as was the group×response interaction (F = 9.109, df = 1, 44, $P < 0.004$). Neither the stimulus×response (F = 2.996, df = 1, 44, n.s.), nor the group×stimulus×response (F = 0.027, df = 1, 44, n.s.) interactions reached the significance level.

The results can be summarized as follows. (1) Irrespective of response modality (V or M), the extinction rate, that is the difference between detection on single and on double stimulation, was significantly higher in RBD than in LBD. (2) Irrespective of the kind of stimulation (S or D), LBD and RBD were affected differently by the change in response modality. Fig. 2 shows that stimulus detection in RBD was worse when a motor, as opposed to a verbal, response was required. This, however, was not true of LBD.

DISCUSSION

Directional hypokinesia

In RBD patients, the detection of single stimuli contralateral to the lesion was found to be significantly worse when monitored by motor reactions with a directional component opposite the side of the lesion. Taken out of context, this would seem to support the directional hypokinesia hypothesis of Watson *et al.* (1978). The finding cannot be explained on a sensory basis alone, since the left key, although located in the affected visual field prior to exploratory ocular movements, was *always* found and pressed whenever single stimuli requiring leftward responses appeared in the (normal) right visual field. In the RBD, impaired detection of left single stimuli with responses contralateral to the lesion might therefore be partly due to premotor factors. However, the absence of a similar effect in the condition of double stimulation leaves the issue of directional hypokinesia open.

Verbal vs motor monitoring of stimuli

The most intriguing result of the experiment is the dissociation in the performance with verbal and motor responses which we found in RBD patients. It must preliminarily be noted that the very high rate of extinction shown by the RBD in the condition M cannot be attributed to motor perseveration—remember that extinction resulted in faulty 'go' responses—since it was paralleled by a reduced number of appropriate 'go' responses to contralesional single stimuli in the same condition. Since this finding was not expected, our interpretation of it is necessarily post hoc. It is not ad hoc, however, insofar as it fits in preexisting empirical and theoretical frames. These will presently be considered and an explanation of our findings will be attempted on their basis. Some implications of such findings relative to the mechanisms of perceptual awareness will then be indicated.

Even in apparently very simple stimulus-response couplings such as those exemplified in our experiment, the neural space intervening between stimulus and response allows for complex modulation. Preliminary to the production of our subjects' responses is the organization of the sensory input into a pattern of neural activity, a perceptual hypothesis, as it were, on which the response is based and which is likely to be influenced, among other things, by the nature of the required response.

In order to explain varying patterns of hemisphere dominance found in normal subjects with simple and choice reaction times, we have argued elsewhere (Vallar *et al.*, 1988) that the relative participation of each hemisphere in associating a given stimulus with a given response depends on the complexity of the events which transact the association.

With simple uncrossed reactions to simple lateralized stimuli (i.e., when the stimulus-response path does not have to cross the corpus callosum), the coupling is likely to be largely a within-hemisphere business. Simple unimanual reaction times to unstructured lateralized stimuli support this opinion (*see* Vallar *et al.*, 1988).

Choice responses, such as those involved in the present situation, are not so straightforward. Here both hemisphere participate in the sensory analysis required to produce differential responses in the presence of one, two or no stimuli. The differentiation between the 'go' and the 'no-go' configurations, in fact, is made on the basis of what each hemisphere detects in its own hemifield, on each trial. Two questions therefore arise: (1) how do the two hemispheres interact in processing stimulus information and (2) to what extent are the results of this joint analysis represented within each hemisphere?

Let us first consider a situation in which a normal subject is exposed to stimuli similar to those employed in the present experiment, without being required to give responses of any kind. Here we have a condition in which, other things being equal, there seems to be no reason to postulate any hemisphere bias in carrying out the sensory analysis and registering its immediate results. Registration of these results may be viewed as corresponding to the commonsense notion of perceptual awareness and implying readiness to initiate whatever reactions happen to be *customarily* associated with the stimuli (e.g., naming or communicating by gesture what the subject has seen). Prior prompting of the subject for a response of *this* kind on each trial is unlikely to introduce radical changes.

A rather different and much more artificial situation is created if the subject is asked to produce differential reactions to elementary stimuli with an *unprecedented* and *totally arbitrary* kind of coupling, as it has been done in the motor condition of the present experiment and in the above-mentioned reaction time studies (Vallar *et al.*, 1988). The results of the latter indicate that in this case the left hemisphere plays a major role in mediating the stimulus-response association. In these studies, as in the motor condition of the present experiment, subjects were asked to press a button in response to single lateralized stimuli (dots) and to refrain from responding to double stimuli or on trials in which no stimulus occurred. We suggested that in this unnatural 'go no-go' situation the assignment of a given reaction to a particular stimulus configuration implies, on each trial, the execution of a sentence-like algorithm; a task which is likely to be within the repertoire of the specific (if not exclusive) left hemisphere competences. Whether or not this is a correct explanation, the *empirically ascertained* location of the core stages of these stimulus-response interconnections in the left hemisphere may help to explain the verbal-motor dissociation found in the detection of single and double visual stimuli in RBD subjects. The explanation may be couched in terms of Kinsbourne's theory of hemisphere activation (Kinsbourne, 1970, 1973, 1975, 1987).

Kinsbourne views the lateral direction of attention as the result of a system in which opposed vectors are contributed by the two cerebral hemispheres. The left hemisphere vector is assumed to be physiologically stronger than that of the right hemisphere. Damage to one hemisphere involves a failure of the corresponding (contraversive) vector, so that the attentional balance is shifted towards the side of the lesion by the unopposed action of the antagonist. Assuming other factors to be equal, attention is in this case unequally distributed between two horizontally separate areas, irrespective of their absolute location in egocentric space. On the contrary, selective engagement of one hemisphere in certain activities enhances the attentional vector of that hemisphere at the expense of the vector dependent on the opposite hemisphere. The empirical support enjoyed by this aspect of the theory is exemplified by the following experiment (Kinsbourne, 1975, p. 83). Normal subjects had to detect gaps in either vertical side of squares projected tachistoscopically in central vision or to either side of the fixation point. In a condition in which no additional task requirements were set, no differences were found in accuracy of detection relative to the side of the gap or to the position of the square in the visual field. When a concurrent verbal task was added, the overall performance did not change, but a rightward attentional bias emerged, which affected detection 'both as regards gap location and as regards position of the square, holding gap location constant'.

Given the results of our reaction time experiments in normal subjects and according to the hemisphere activation hypothesis, the selective engagement of the (unlesioned) left hemisphere in the execution of the 'go no-go' algorithm in the motor response condition of the present experiment should generate a much greater right-orientated attentional bias than for a semiautomatic and cognitively nondemanding activity such as naming the number of the stimuli. In RBD subjects this would add to the imbalance independently created by the right hemisphere lesion and aggravate the detection inaccuracy as regards left stimuli. This is indeed what we found in our experiment.

It might be contended that, were this explanation true, in the LBD group left hemisphere activation during the execution of the 'go no-go' algorithm should be expected to improve the detection of right stimuli in condition M with respect to condition V, which, as shown in fig. 2, is not the case. It must, however, be considered that, in this group, the existence of a lesion in the hemisphere which in normal subjects has been shown to be selectively involved in the execution of the 'go no-go' algorithm precludes any such inferences.

It must also be considered that whatever are the reasons for the differences that we found in the performance of LBD and RBD patients, there is no guarantee that such differences are due to functional hemisphere asymmetries. Although clinical and radiological data did not suggest obvious discrepancies between the two groups of patients, the exclusion of severe dysphasics from the LBD group constitutes a distinct bias.

Nonetheless, it is worth noting that although the detection of single contralesional stimuli in the verbal condition was actually poorer in LBD than in RBD patients, the rate of extinction was much greater in the latter group. Whether or not it reflects hemisphere asymmetries, this finding definitely shows that the phenomenon of extinction cannot simply be explained in terms of heightened sensory thresholds.

Impaired detection of contralesional stimuli as a failure of access to consciousness

In our RBD cases, response modality had a crucial influence on the awareness of contralesional stimuli. This suggests that the sensorimotor interface is deeply involved in the production of conscious mental content. It is still impossible to state whether and to what extent response factors modulate perceptual awareness at this particular stage, or whether awareness is subjected to other vicissitudes further along the stimulus-response chain. This is a most intriguing facet of the issue, since it draws attention to diachronic aspects of consciousness which are seldom considered. Some response factors might indeed operate downstream, such as directional hypokinesia, provided it proves to be a reliable construct. The question therefore arises as to whether response mechanisms might divest of consciousness mental contents which had already reached neuronal adequacy.

Extravagant as it may at first appear, the hypothesis of a secondary dismantlement of conscious mental states by response factors is forced on us by some observations made on left hemineglect patients engaged in a visuomotor task employing the same apparatus as shown in fig. 1. In this experiment too (Bisiach *et al.*, 1985), each trial was initiated by the examiner's command asking the patient to press the central button with the forefinger of his right, ipsilesional hand. This caused a 200 ms flash of light to be emitted by a red diode (upper row in the front panel) or green (lower row) diode. At the same time, two responses keys of different colours (red/green) lit up, one on each side of the panel, red on the left and green on the right, or vice versa. The patients had been instructed to press the response key of the same colour flashed by the diode, irrespective of the side. Depending on the position of the stimulus and of the appropriate response key there were therefore four stimulus-response conditions, two crossed and two uncrossed (left-left, left-right, right-left, and right-right). As expected, patients missed a variable number of left (contralesional) stimuli. The rate of omission errors, however, was higher when they had to respond by pressing the left (contralesional) rather than the right key in order to match the colours of the diode and of the response key according to instructions.

Even more interesting was the patients' behaviour on trials with right stimuli, that is, with stimuli falling in the half-field unaffected by the lesion. When the appropriate response key happened to be on the *right* side their performance was virtually errorless. On the other hand, when the response was related to the *left* key, part of the stimuli went apparently undetected. The phenomenon was particularly striking in a patient with a right vascular lesion involving the deep structures of the frontal lobe, the head of the caudate nucleus and the internal capsule. This patient correctly reacted to all right stimuli requiring a right response, but did not react to 50% right stimuli requiring a left response. On several occasions, the patient spontaneously declared that no stimulus had occurred, although a diode had actually flashed in the *unaffected* half-field (which shows that the patient had not simply withheld a motor response once having failed to find the appropriate key, when the latter was located in the neglected side of space).

This is not merely a dramatic illustration of how deeply response factors can influence perceptual awareness. Indeed, the kind of response was not, in this experiment, fully predetermined, but had to be computed, on each trial, over a property of the stimulus itself, namely the colour of the flashing diode. Therefore 'nonpreferred' (contralaterally directed) responses must have interfered with consciousness after a stage at which information about the stimulus was already such as to guide the search for the appropriate key, that is, after a stage at which commonsense would hold such information to be conscious.

To summarize and conclude, the phenomena that we have considered in this paper suggest that the properties of perceptual awareness are established stepwise and restructured through lookahead and backtracking processes developing at the level of a still loosely defined stimulus-response interface. They also suggest that the mechanisms which confer conscious properties to mental contents might not be single but include selections occurring at a merely perceptual level (Marcel, 1983), as well as selections related to the actions an organism is going to perform on the basis of information currently processed by the brain (Shallice, 1972, 1978; Allport, 1988).

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COGNITIVE EVENT-RELATED POTENTIALS IN MULTIPLE SCLEROSIS

by M. R. NEWTON,[1]* G. BARRETT,[1] M. M. CALLANAN[2] *and* A. D. TOWELL[1]

(From the [1]*Medical Research Council External Scientific Staff and* [2]*Psychology Department, The National Hospital, Queen Square, London)*

SUMMARY

Twenty-three patients with multiple sclerosis (MS) and 1 patient with isolated optic neuritis (mean age 37.5 yrs, average duration of disease 10 yrs) were tested with auditory and visual cognitive event-related potentials (ERPs) using an oddball paradigm. The results were compared with data from 19 age-matched healthy controls. All patients had magnetic resonance imaging (MRI) head scans and 19 had comprehensive neuropsychological testing. The stimulus-related components of the ERPs were normal for nearly all patients, but 10 showed abnormalities of the later cognitive-related components and another 3 had waveforms in which the cognitive components could not be identified. These abnormalities were found mainly for the auditory test. Of these 13 patients, 11 had significantly prolonged reaction times (RT) or reduced target recognition performance. Five of 8 MS patients with normal IQ and memory function tests had abnormal ERPs with the reverse being true for 4 of 10 patients. Patients with abnormal ERPs showed a higher MRI cerebral lesion score and had a longer duration of illness and greater physical disability than patients with normal ERPs. It is concluded that the generation of ERPs is in part dependent on the integrity of cerebral white matter and that ERPs may indicate subtle degrees of cognitive dysfunction not always detected by standard tests of intellect.

INTRODUCTION

Alterations in cognitive function in multiple sclerosis (MS) have been increasingly studied over the last three decades. Although Charcot (1877) and Gowers (1892–1893) noted the frequency of memory problems in their patients, more systematic studies of memory and other cognitive processes have since been published (e.g., Ross and Reitan, 1955; Jambor, 1969; Reitan *et al.*, 1971; Beatty and Gange, 1977). These studies reported impaired recall of verbal and nonverbal material, reduced ability to abstract and difficulty in performance of motor and perceptuomotor tasks. These deficits were found in patients with long-standing disease, but recently Grant *et al.* (1984) discovered similar memory problems in patients with a shorter duration of illness, suggesting that unrecognized memory impairment may be common early in the natural history of the disease. They also suggested that these problems may be associated with an episode of relapse.

In addition to the cognitive defects, affective disorders such as depression and mood swings in MS patients are well recognized (Cottrell and Wilson, 1926; Surridge, 1969; Kahana *et al.*, 1971; Ron, 1986). Such disorders appear to be found with increasing

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* Present address: Neurology Dept., Austin Hospital, Heidelberg, Victoria 3084, Australia.

Correspondence to: Dr G. Barrett, Medical Research Council, The National Hospital, Queen Square, London WC1N 3BG, UK.

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frequency in patients with a longer duration of illness who also show more evidence of structural brain disease as demonstrated on CT (Rabins *et al.*, 1986) and MRI (Huber *et al.*, 1987) brain scans.

Electrophysiological investigations of central nervous function in demyelinating disease are at present mainly confined to visual, auditory and somatosensory evoked potentials which occupy an established role in the diagnosis of MS by providing evidence of subclinical disease in the visual, auditory and posterior column sensory pathways, respectively (Halliday, 1982). Event-related potentials (ERPs) evoked during target detection tasks have been studied extensively since they were first reported in the mid-1960s (Sutton *et al.*, 1965). The main component of interest has been a large positivity occurring some 300 ms after an infrequent auditory tone presented randomly with tones of a different pitch in what is commonly called the 'oddball' paradigm. This component, named P300 or P3, is not modality-specific and is generally evoked by low probability events in tasks where a subject has to discriminate between stimuli. In the auditory modality P3 is preceded by an N1 at approximately 100 ms, P2 at 200 ms and N2 at an average of 250 ms (Picton and Hillyard, 1974) and followed by a slow-wave (SW) which is negative-going frontally and positive-going posteriorly (Squires *et al.*, 1975). The first 2 of these components appear to reflect both sensory and cognitive aspects of the evaluation of an auditory stimulus with at least 6 separate brain processes (including sensory factors, attention and ease of discrimination) thought to be responsible for determining component latency, amplitude and distribution (Näätänen and Picton, 1987). The number and latency of components preceding N2 and P3 in tasks of visual cognition tend to be determined by stimulus characteristics of size, luminance, contrast, etc., so there is not as much uniformity in component naming between studies as there is for auditory tasks. Thus the 'early' visual components tend to be named according to their polarity and latency rather than sequential order as used for auditory components. The amplitude of the N2 component has been related to ease of discrimination between stimuli (Fitzgerald and Picton, 1983) with N2 amplitude increasing as discrimination becomes more difficult. However, larger N2 components tend to be associated with longer P3 latencies (G. Barrett and A. Starr, unpublished observations) so it may be that N2 for easy discriminations is hidden by the downgoing limb of a correspondingly early P3 component. A more difficult discrimination may lead to a later P3 resulting in a larger N2 due to the unmasking of this component. The amplitude of P3 in the oddball task is inversely related to stimulus probability and the latency is generally considered to reflect stimulus evaluation time (*see* Pritchard, 1981, for a review of the relationship between P3 and cognitive factors). The slow-wave has not received a great deal of attention but may reflect nonspecific activation processes (Rohrbaugh *et al.*, 1979).

The association between P3 latency and stimulus evaluation time suggested a possible application for ERPs in the study of dementia. Some workers have found P3 latency in an oddball task to be abnormally prolonged in patients with Alzheimer's disease (Goodin *et al.*, 1978*b*; Syndulko *et al.*, 1982; Pfefferbaum *et al.*, 1984*b*; St Clair *et al.*, 1985; Gordon *et al.*, 1986; Neshige *et al.*, 1988). Others have found ERP abnormalities in the 'subcortical' dementias associated with Parkinson's disease (Hansch *et al.*, 1982) and Huntington's disease (Lawson *et al.*, 1984; Hömberg *et al.*, 1986). It has also been suggested that these potentials could be of value in distinguishing different subtypes of dementia (Goodin and Aminoff, 1986) and that they are abnormal in various psychiatric conditions (Gordon *et al.*, 1986; Pfefferbaum, 1986; Blackwood *et al.*, 1987). Given the frequency of cognitive deficit in MS patients, we studied long-latency event-related potentials (ERPs) in 23 patients with MS and 1 with optic neuritis in an attempt to discover what abnormalities, if any, were evident and if so whether they correlated with the clinical and MRI brain scan data and with the scores from other tests of cognitive function that were available for these patients.

PATIENTS AND METHODS

All patients included in this study had earlier undergone clinical and investigative evaluation of their disease at the National Hospitals for Nervous Diseases. Twenty-three of the 24 patients studied had clinically definite MS and 1 had isolated optic neuritis (Case 10); 16 were female and the mean age for all patients was 37.5 (range 26–58) yrs. The average duration of disease was 10 (range 2–23) yrs. Clinical details for each patient are contained in Table 1. The spectrum of physical disability extended from 0 to 8 on the Kurtzke 10-point disability scale (Kurtzke, 1955). An estimate of premorbid intellectual functioning was obtained using the National Adult Reading Test (Nelson, 1982) and current intellectual functioning

TABLE 1. CLINICAL INFORMATION AND MRI SCORES

Case no.	*Age (yrs)*	*Sex*	*Duration (yrs)*	*Kurtzke score*	*History of affective illness*	*IMC (MMS)*	*MRI score*	*% PVL*
1	33	M	6	3		38	6	100
2	34	F	3	0		[29]	14	86
3	52	M	22	3		38	28	64
4	28	F	2	1	Depressed	36	20	70
5	31	M	15	6		38	35	60
6	58	F	23	3	Depressed	38	4	50
7	35	M	5	0		38	3	67
8	26	F	5	2		36	23	48
9	38	F	9	3		38	37	65
10	26	F	2	0		38	0	0
11	55	F	20	8	Depressed	30	39	67
12	39	F	2	0		37	3	67
13	46	F	12	6		38	33	61
14	28	F	11	3		38	28	71
15	29	F	12	0	Depressed	35	24	67
16	50	F	12	4	Depressed	37	18	78
17	42	F	6	7	Depressed	[26]	9	78
18	31	M	9	6		38	36	61
19	37	F	14	6	Depressed	36	40	65
20	56	M	20	5		[29]	25	60
21	29	M	11	7	Depressed	38	33	58
22	28	M	5	7		[30]	46	54
23	36	F	5	5	Depressed	24	54	56
24	33	F	3	6	Depressed	38	17	71

Duration = disease duration; Kurtzke score = Kurtzke Disability Score (Kurtzke, 1955); IMC = Information-Memory-Concentration Test of Blessed *et al.* (1968), maximum score 38; MMS = Mini-Mental State, maximum score 30 (Folstein *et al.*, 1975); MRI score was computed using the method described by Ormerod *et al.* (1987); PVL = periventricular lesions.

was assessed using the Wechsler Adult Intelligence Scale (British adaptation by Saville, 1971). A measure of intellectual deterioration was obtained by subtracting the patient's current full scale IQ from the estimated premorbid score. A discrepancy of 13 points or more (obtained in <5% of the normal population) was the criterion for identifying a significant degree of intellectual deterioration. A measure of memory for verbal and visual material was assessed using a recognition memory test (Warrington, 1984). Patients scoring below the fifth percentile on either the verbal or the visual version of the test were identified as having a corresponding memory deficit. (These tests were not administered to 5 of the 24 patients—Cases 2, 3, 8, 21 and 24.) Ten patients had a history of significant depression during their illness but none was depressed or taking antidepressant medication at the time of the study. A short questionnaire (the Information-Memory-Concentration Test of Blessed *et al.*, 1968) was administered to 20 patients immediately before ERP testing. This test is designed to give a brief assessment of each patient's mental state (attention, short and long-term memory, etc.). The other 4 patients had been tested with the Mini-Mental State test (MMS) of Folstein *et al.* (1975) on an earlier occasion. MRI brain scans on all patients were quantified from examination of a multislice protocol (Ormerod *et al.*, 1987) with lesions being considered as either periventricular or discrete in location. The periventricular area was divided into 7 parts: body of lateral ventricle, frontal horn, trigone, occipital horn, temporal horn, third ventricle and fourth ventricle. Lesions in each area were scored 0 to 3 depending on their size as measured by the maximum degree of penetration from the edge of the ventricle into the surrounding white matter (0 = no lesion, 1 = up to 5 mm penetration, 2 = 6–10 mm, 3 = >10 mm). Discrete lesions separate from the ventricles were scored according to their size as above for each of 8 sites: brainstem, cerebellum, internal capsule, basal ganglia, frontal lobe, parietal lobe, temporal lobe and occipital lobe. The scores from all 15 sites in both hemispheres were then added to give the total score for each patient. Scans were independently scored by 2 observers providing an inter-rater reliability of 0.95.

The patient ERP data were compared with those obtained from 19 healthy control subjects of the same age range (mean age 37.6 yrs) and a separate control group including a further 10 subjects to give a total age range of 19–82 yrs. Informed consent to participation in these experiments was obtained from all patients and healthy controls. Subjects were presented with an auditory 3-stimulus target detection task followed by a similar test in the visual modality (*cf.* Pfefferbaum *et al.*, 1980). On each trial of the auditory task the subjects heard through headphones either a 2 kHz tone (target, $P = 0.15$), a 1 kHz tone (infrequent nontarget, $P = 0.15$) or a 1.5 kHz tone (frequent, $P = 0.70$). Subjects were required to press a hand-held push-button with their right thumb as quickly as possible whenever they heard a target tone. Tones were 50 ms in duration with rise and fall times of 10 ms. The interstimulus interval was 1.2 s. For each trial of the visual task, 1 of 3 letters was displayed in the centre of a television monitor placed 1.5 m in front of the subject. The letter 'X' was the target stimulus and the letters 'O' and 'T' were the infrequent nontarget and frequent stimuli, respectively. The stimuli subtended a visual angle of 12 min horizontally by 15 min vertically and stimulus duration was 100 ms. Stimulus probabilities, response requirements and interstimulus interval were the same as for the auditory task. A 3-stimulus test rather than a 2-stimulus task was used as it provides waveforms for a rare stimulus uncontaminated by brain potentials associated with making a motor response.

A number of practice trials were presented before each task to ensure that the subjects were responding correctly and were able to distinguish between the tones in the auditory test and identify the letters in the visual task. If subjects were unable to make these distinctions then either stimulus duration was lengthened or the pitch of the target tone was increased. Subjects who had difficulty seeing the small visual stimuli were moved closer to the screen. These adjustments in stimulus presentation were made until the experimenters and the subject were satisfied that the task could be performed accurately. In one case visual acuity was so poor that the visual ERP test could not be performed. Stimuli were presented from predetermined tables of randomly ordered trials until either a total of 25 artefact-free responses to target trials had been averaged or a total of 200 stimuli had been delivered. Three such runs were presented for each modality unless excessive eye movements reduced the number of target responses to below 50, in which case a fourth run was presented. (This procedure was adopted for all the patients and all but

7 of the control subjects who had been involved in a previous study in which 2 runs of 20 artefact-free target responses was the acceptance criterion.)

Event-related potentials were recorded from silver/silver chloride disc electrodes fixed to the scalp at locations Fz, C3, Cz, C4, P3, Pz and P4 referred to linked electrodes fixed to the earlobes. Eye movements were monitored by recording between an electrode on the outer canthus of the right eye referred to an electrode on the glabella. Responses which included eye movement activity exceeding 100 μV were excluded from the averages. The electrical activity from each of these 8 channels was sampled at 3.75 ms per ordinate for a total duration of 960 ms beginning 120 ms prestimulus. The amplifier time constant was 3 s with a high frequency cut-off 3 dB down at 5 kHz. The activity associated with each individual trial was stored on digital magnetic tape along with the reaction time (RT) if the subject pushed the response button. Averages for target, infrequent nontarget and frequent stimulus presentation were also stored on tape. Stimulus presentation and response averaging were controlled by computer. Any averages judged to contain excessive eye movement artefact (e.g., from signals less than 100 μV but time-locked to the stimulus) were reaveraged using the individual trials from the magnetic tape. Each single trial was inspected visually and rejected from the average if the activity in the eye-monitoring channel showed evidence of an eye movement. Automatic rejection of trials on which an incorrect behavioural response occurred was not possible so the reaveraging procedure described above was also carried out if a subject failed to press the button to the target stimulus on an excessive number of trials (>20%). This ensured that the averages for target trials of subjects with poor performance only contained responses associated with correct identification of the stimulus.

Averages were filtered digitally with a high frequency cut-off at 30 Hz before cursoring or plotting. Components were identified according to their polarity, latency and distribution across the scalp. Latencies of components N1, P2, N2 and P3 were measured in the averaged responses to auditory targets and infrequent nontargets. N1 was taken as the most prominent negative peak in the range 75 to 140 ms, P2 was the most prominent positive peak between 140 and 220 ms, N2 was taken as the most prominent negative peak between P2 and P3 which in turn was identified as the most prominent positive peak occurring after 270 ms. In the visual responses a positivity at an average latency of 160 ms (P160), a negativity averaging 200 ms (N200) and a positivity averaging 250 ms (P250) were identified as the most consistent 'early' components occurring across subjects. The visual N2 was defined as the most prominent negative peak between P250 and P3 and the lower latency limit for P3 in this modality was taken as 350 ms. The amplitudes of these components along with a slow-wave (SW) in each modality were measured with respect to the mean of the activity occurring during the 120 ms prestimulus baseline period. The peak of the slow-wave was identified in the Fz channel and the amplitude values for this component were measured at the same latency in each channel. Measurements were made independently by 2 of the authors (G.B. and A.D.T). There was a high level of agreement between the 2 sets of measurements. Because of reported changes of ERP measures with age (Goodin *et al.*, 1978*a*; Brown *et al.*, 1983; Pfefferbaum *et al.*, 1984*a*; Picton *et al.*, 1984; St Clair and Blackwood, 1985; Gordon *et al.*, 1986; Barrett *et al.*, 1987) and the importance of using age-related normal values in the event of such a relationship, systematic changes of component latency or amplitude with age were assessed in the larger group of 29 control subjects using polynomial regression (program BMDP5R of the BMDP Statistical Software package, Dixon, 1983). Response performance was assessed using the mean RT to target stimuli, the percentage of correct responses to target presentation (% hits), the percentage of responses to infrequent nontarget stimuli (% nontarget false alarms) and the percentage of responses to frequent stimuli (% frequent false alarms).

The choice of criteria to be used for assessing the normality of observed results from individual patients presents a problem for studies in which the observed values in the control population may change with age. This choice becomes even more difficult if the relationship between the measured variable and age is nonlinear. Brown *et al.* (1983), for example, have argued that the correlation between P3 latency and age is nonsignificant below 45 yrs but changes to a highly significant relationship above this age. St Clair and Blackwood (1985) argued that the slope of this relationship increases after the age of 53 yrs and Gordon *et al.* (1986) found that the increase in gradient occurred some 10 yrs later at 63 yrs. When studying a group of comparatively young patients, as in this study, the choice of criteria for abnormality is particularly difficult. We have therefore assessed the results for each individual patient in two ways, first, by comparison with the corresponding mean ± 2.5 SD measured from the age-matched control group and secondly, by comparison with confidence limits computed 2.5 SDs on either side of the linear regression line relating the tested variable to age as measured from the group of 29 control subjects whose ages ranged from 19 to 82 yrs. Results for individual patients were only considered abnormal if they were beyond normal limits for both of these criteria.

RESULTS

Control subjects

Reaction time performance

Means and SDs for RTs and accuracy of performance are shown in Table 2. RTs were similar for the two modalities although the within-subject SD of RT was considerably smaller in the visual modality. There was also a higher proportion of hits and a lower proportion of false alarms for the visual task, suggesting that subjects found this test easier than the auditory task. There were no significant linear or curvilinear relationships between mean RT and age.

Event-related potentials

Reaveraging of single trial waveforms was not necessary either for removal of residual eye movement artefact or for exclusion of trials associated with incorrect behavioural responses. For the auditory task the mean number of sweeps in the averages for the target stimulus was 55 (range 40–75), including a mean of 1.9 trials associated with incorrect behavioural responses (range 0–7). The corresponding figures for the infrequent nontarget stimulus were 50 (range 23–69) and 0.4 (range 0–2) and for the frequent stimulus 257 (range 140–357) and 0.5 (range 0–5). In the visual task the mean number of sweeps in the averages for the target stimulus was 57 (range 40–75), including a mean of 0.6 trials associated with incorrect behavioural responses (range 0–5). The corresponding figures for the infrequent nontarget visual stimulus were 50 (range 36–68) and 0 and for the frequent visual stimulus 246 (range 168–339) and 0.

TABLE 2. MEANS AND STANDARD DEVIATIONS FOR REACTION TIME PERFORMANCE BY CONTROL SUBJECTS

	RT (ms)	*SD RT (ms)*	*% hits*	*% nfa*	*% ffa*
Auditory					
Mean	443	97.4	95.4	0.9	0.3
SD	64.5	27.0	6.7	1.6	0.7
Visual					
Mean	462	54.6	99.1	0.0	0.0
SD	58.0	15.3	2.2	0.0	0.0

SD RT = mean within-subject SD of reaction time; % hits = percentage of target trials with correct responses; % nfa = percentage of false alarms on nontarget trials, % ffa = percentage of false alarms on frequent trials.

The group average age-matched control and patient waveforms for auditory and visual target stimuli and auditory infrequent nontarget trials (termed 'nontargets' from now on) together with identification of the components measured in this study are shown in fig. 1. Table 3 gives the means and SDs for component amplitudes and latencies for the infrequent stimulus categories in the 2 stimulus modalities. Components which were clearly identified in the responses to visual target stimuli were often difficult to detect in the corresponding nontarget waveforms which tended to resemble the low amplitude responses to frequent stimuli instead. This is in distinct contrast to responses from the auditory modality in which the averages to the two infrequent stimuli bear a close resemblance in terms of morphology and component amplitude. Because of the unreliability of the visual nontarget responses (in terms of component identification) these potentials were not used in assessing the normality of patient data and will not be considered further. All components for auditory stimulation were widespread across the scalp, whereas the early visual components (P160 and N200) were only recorded consistently (in at least 18 of 19 subjects) at the left parietal electrode. Consequently the limits of normality for these 2 potentials were only established for measurements at this electrode site. All other comparisons with patient data were made for measurements in the midline channels Fz, Cz and Pz. Fig. 2 illustrates the superimposed responses from all subjects in the age-matched control and patient groups for the auditory and visual stimuli. The most notable feature both of this illustration and fig. 1 is the comparative absence or reduction in amplitude of the N2 component in the target responses of the patients. Observation of the patient waveforms suggested possibly latency differences between the P3 peaks identified in the 3 midline channels. As can be seen from Table 3 such differences were comparatively small for the control subjects

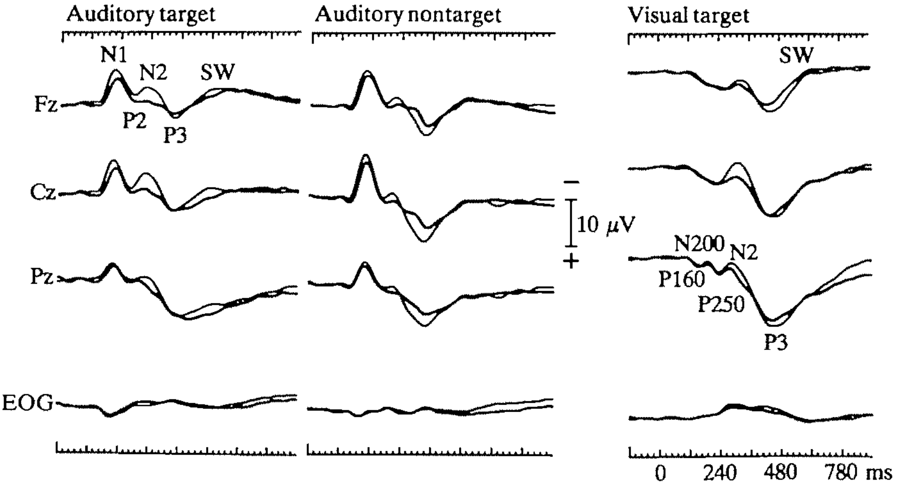

FIG. 1. Comparison of group average waveforms recorded from age-matched normal controls (thin line, n = 19) and patients (thick line, n = 24), together with identification of components measured in this study.

TABLE 3. MEANS AND STANDARD DEVIATIONS FOR ERP COMPONENT LATENCIES (ms) AND AMPLITUDES (μV) FOR CONTROL SUBJECTS

		Fz				*Cz*				*Pz*			
		Target		*Nontarget*		*Target*		*Nontarget*		*Target*		*Nontarget*	
Auditory													
N1	Mean	101	−7.7	103	−8.3	101	−7.7	103	−9.9	101	−4.1	107	−5.9
	SD	13.9	2.3	14.9	3.4	12.5	2.7	10.7	4.0	12.7	2.0	18.8	2.4
P2	Mean	182	−1.2	184	1.1	172	−0.1	183	2.3	180	1.1	180	2.1
	SD	20.8	3.1	29.1	4.5	16.2	3.3	31.1	5.0	24.8	2.9	29.2	3.6
N2	Mean	245	−5.4	236	−3.5	240	−6.6	227	−2.3	237	−2.4	227	−0.5
	SD	32.4	3.8	33.4	4.4	32.0	4.8	31.3	5.8	26.4	3.4	32.2	4.0
P3	Mean	354	4.3	337	7.4	363	5.3	333	10.6	371	9.6	339	10.1
	SD	36.9	4.0	20.7	4.9	47.0	5.0	21.9	6.0	42.3	4.4	27.3	5.6
SW	Mean	563	−6.0	513	−2.8	563	−3.9	513	−0.4	563	2.8	513	1.5
	SD	97.4	4.5	56.9	2.8	97.4	5.5	56.9	4.4	97.4	4.1	56.9	5.1
Visual													
P160	Mean	162	3.0	156	1.4	159	2.0	163	1.9	157	2.6	160	2.7
	SD	24.0	3.0	22.6	2.3	22.8	3.3	21.7	2.4	18.2	2.0	22.3	1.8
N200	Mean	202	+1.7	185	+0.1	188	+1.1	181	+0.4	191	−0.1	197	+0.2
	SD	24.2	3.0	23.7	2.1	24.8	4.0	19.8	2.5	15.5	2.8	17.7	2.2
P250	Mean	266	5.7	232	3.3	249	5.2	231	3.8	246	4.5	238	3.5
	SD	31.4	3.4	28.4	1.5	32.4	3.1	13.7	2.4	23.4	3.1	14.7	2.5
N2	Mean	323	+0.3	311	−0.4	319	−2.9	306	−0.2	300	−0.1	298	+0.3
	SD	39.5	4.7	50.1	2.3	33.9	6.4	51.2	2.6	32.3	4.7	49.0	2.9
P3	Mean	442	10.1	416	3.8	446	12.6	421	6.1	448	17.4	419	5.9
	SD	37.8	5.4	47.7	2.6	36.1	5.7	46.3	3.5	36.5	4.3	47.6	2.7
SW	Mean	645	−2.8	607	−2.0	645	−0.6	607	−0.6	645	4.1	607	−0.3
	SD	77.8	4.8	72.8	2.1	77.8	3.4	72.8	2.7	77.8	4.3	72.8	2.3

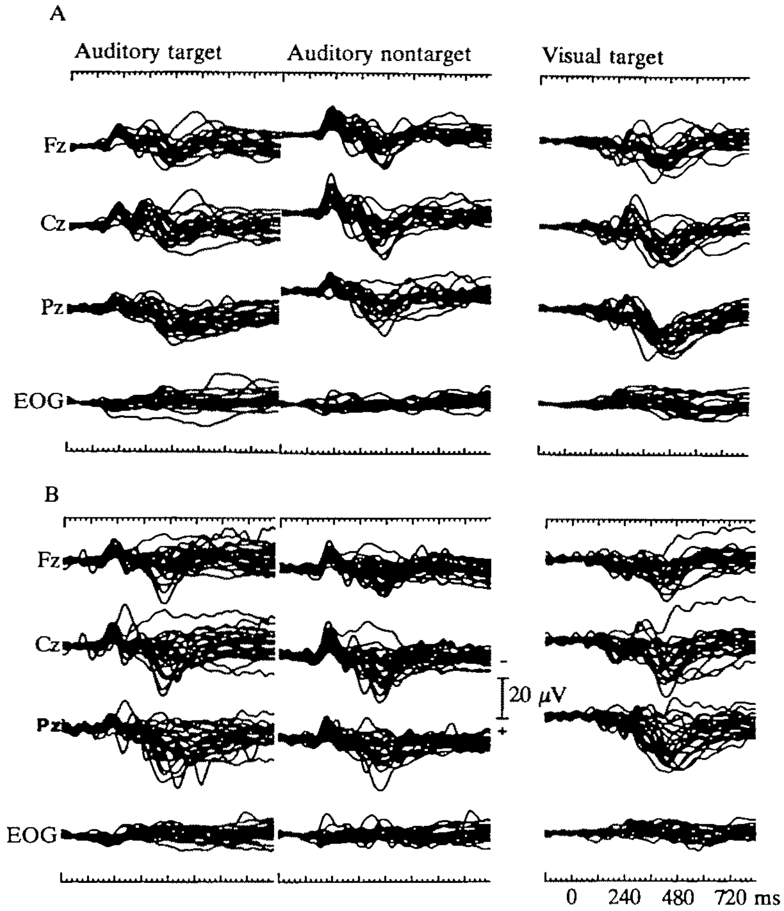

FIG. 2. Superimposed waveforms for each individual in the age-matched normal control (A, n = 19) and patient (B, n = 24) groups.

(maximum mean difference = 17 ms comparing Pz and Fz responses with auditory target stimuli). Means and SDs for such interelectrode comparisons were therefore calculated from the control data so that assessments of normality for patient data could be made.

The regression lines relating P3 latency to age for the larger group of control subjects were significant at Fz, Cz and Pz for auditory target, nontarget and visual target responses. The correlations for auditory nontarget stimuli were comparatively high with values of 0.69, 0.66 and 0.77 for Fz, Cz and Pz, respectively (all $P < 0.001$). Otherwise only one correlation exceeded 0.5 (auditory target at Fz, $r = 0.51$, $P < 0.01$). Scattergrams, regression lines and confidence limits for auditory target, nontarget and visual target P3 latencies measured at Pz are shown in fig. 3. The upper limit of normal latency computed from the age-matched control data is included for comparison. Three conditions showed a significant reduction of P3 amplitude with age (auditory target at

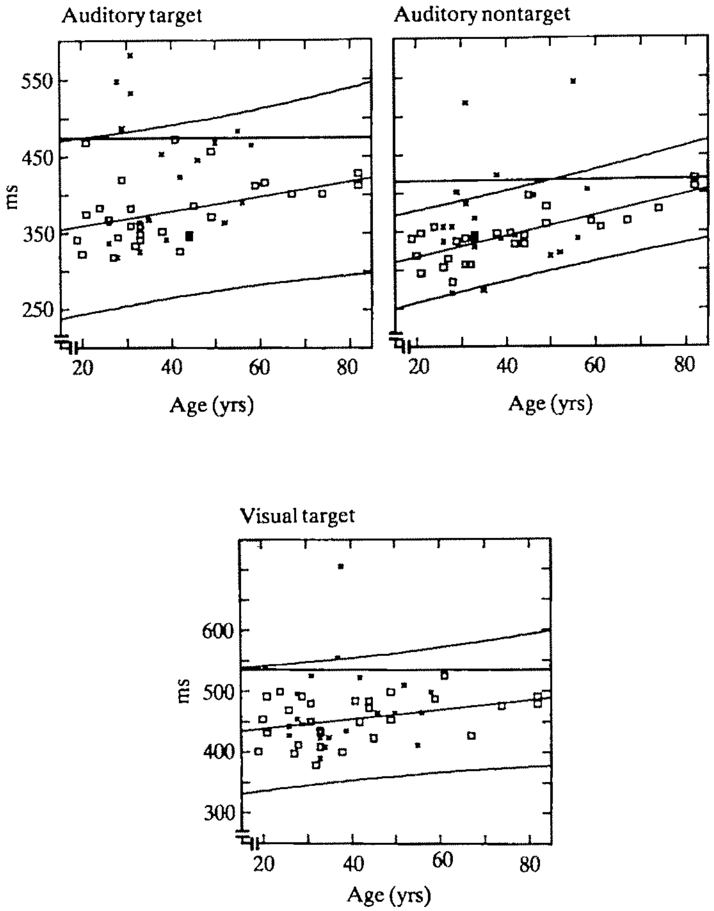

FIG. 3. Scattergrams showing relationship between P3 latency measured at Pz and age for auditory target, auditory nontarget and visual target responses as computed from a group of 29 healthy individuals aged 19–82 yrs (square symbols) and MS patients (crosses). Linear regression lines are shown together with 99% confidence limits and the upper limit of normal (horizontal lines) as calculated from the mean + 2.5 SDs for data obtained from the 19 healthy controls with the same age range as the patients. Individual data points for patients and controls are shown. Note that it was not possible to obtain latency values for all patients. Slope, intercept, correlation coefficient and significance values for the regression lines were: auditory target 0.96 ms/yr, 340 ms, 0.41, $P < 0.05$; auditory nontarget 1.35 ms/yr, 291 ms, 0.77, $P < 0.001$; visual target 0.77 ms/yr, 423 ms, 0.37, $P < 0.05$.

Cz and Pz, visual target at Pz; all $P < 0.05$). Auditory target N2 latency measured at Pz was also significantly correlated with age ($r = 0.60$, $P < 0.001$). The amplitudes of auditory and visual target slow wave amplitudes measured at Pz decreased with age ($P < 0.05$). None of the other component measures showed significant linear relationships with age. The statistical analysis showed no significant curvilinear relationships and examination of scattergrams plotted for control subjects' data suggested no obvious discontinuities in the relationships between component measures and age.

Patients

Tests of cognitive function

The patient with optic neuritis showed no evidence of intellectual deterioration or deficient verbal or visual memory function. Of the 18 MS patients who were assessed with the tests of cognitive function, there was a significant degree of intellectual deterioration in 6 (Cases 4, 11, 13, 17, 19, 23). In 3 of these patients (Cases 4, 11, 17) there was also a significant impairment in performance on both verbal and visual versions of the recognition memory test. One further case with significant intellectual deterioration (Case 19) had a significant deficit on the visual version of the memory test alone. The only other evidence of memory deficit in this group was a significant degree of visual memory deficit in 4 patients (Cases 9, 12, 14, 20) in whom there was no evidence of intellectual deterioration.

Reaction time performance

There was a comparatively high error rate for failure to respond to target trials, whereas the proportion of false alarms was low and no different from that for the control group. Mean RTs and the percentage of hits for target trials are given for each patient in Table 4. The group mean values (and SDs) for these 2 measures were 479 ms (111.9 ms) and 79.4% (24.5%) for the auditory modality and 526 ms (119.5 ms) and 85.8% (21.3%) for the visual modality. Both of these measures of RT performance were significantly more variable for the patient group than the controls. Comparison of these results with the corresponding values for control subjects given in Table 2 was done using Mann-Whitney U tests with correction for ties (Siegel, 1956). This nonparametric test was used rather than the independent t test because the significant differences in variability of data from the 2 groups violates the assumptions of the latter test. The tests showed no difference between patients and controls for the mean RTs and auditory hit rate. The hit rate in the visual test was significantly worse for patients than controls ($P < 0.02$). The comparatively large SDs for patient RTs, coupled with the lack of difference from the control values, suggests that the patient data are bimodal. Table 4 indicates that this is indeed the case with a number of patients showing abnormally prolonged RTs and others showing quite normal values.

Three patients had abnormal RTs and performance in the auditory task and a further 6 had abnormal performance scores alone. In the visual modality, 6 patients were abnormal on both RT measures, whereas only 1 patient had an abnormal performance score alone. Five cases had abnormal RT measures for both modes of stimulus presentation.

Event-related potentials

The incidence of eye movement artefact remaining in the averaged waveforms was rare although in one striking example (Case 6) the P3 component recorded at Fz was not only smaller after off-line correction but also shorter in latency. The latency decrease

TABLE 4. REACTION TIME AND EVENT-RELATED POTENTIAL MEASURES FOR EACH PATIENT TOGETHER WITH AN INDICATION OF NORMALITY

	Auditory								Visual				
			Target			Nontarget					Target		
Case no.	RT (ms)	% hits	N2 (ms)	P3 (ms)	SW (μV)	N2 (ms)	P3 (ms)	SW (μV)	RT (ms)	% hits	N2 (ms)	P3 (ms)	SW (μV)
10	443	96	217	337	9.6	259	337	2.5	478	97	262	442	12.2
12	364	100	206	341	13.3	217	341	7.7	451	99	292	435	8.5
7	315	100	229	367	5.2	221	274	0.2	383	100	285	424	3.5
6	542	98	(322+) **	(469#) ***	15.9	232	405+	(4.3#) **	483	100	360	499b	21.6 ***
1	373	100	217+	364	3.7	247	367	−0.1	387	100	274+	390	2.9
17	434	81	259	424b	−3.1	289	345	−2.0	576	72 ***	262	521b	2.8
2	460	76 **	214a	469a	15.1a	236a	409a	9.8a	432	100	281	409	(15.6) **
24	315	100	195	326	3.1	275	330	2.7	395	100	300	424	12.6
16	550	68 ***	300#	469	6.0	206	319	4.5	509	99	259	465	14.0
4	356	99	172	319	13.1	311	356	7.9	466	100	270	454	9.9
8	433	94	236	364	5.9	206	356	0.0	407	100	266	427	8.7
15	557	88	296	487 **	1.5	270	[401]	2.7	539	96	263+	446	3.5

20	388	99	229	390	3.0	225	341	2.9	447	100	292	465	4.8
14	422	99	380 # ***	547 ***	8.4	281 #	270	1.0	427	100	424 ***	540+ **	(16.5) **
3	315	100	191 #	364	4.1	202 #	322	−1.4	439	100	330	510b	10.4
21	655 ***	25 ***	M	M	M	M	M	M		Not tested—poor acuity			
13	598	95	289	446	2.6	292	397	−0.8	557	99	319	465	−1.5
5	495	54 ***	386 ***	581 ***	5.9	M	517 ***	−2.7	538	96	(386) **	525	5.7
18	570	63 ***	M	552 ***	2.0	M	386	−1.4	772 ***	33 ***	Too few sweeps		
9	444	99	345 ***	454	7.7	349 ***	424 ***	6.8	674 ***	52 ***	469 ***	705 ***	10.7
11	629 **	61 ***	(330) ***	(484) **	−4.1	277	544 ***	4.1	698 ***	62 ***	360	412c	(−8.0) **
19	588	37 ***		Too few steps		M	M	M	644 ***	64 ***	480 ***	555 ***	8.1
22	[600]	55 ***	M	M	M	M	M	M	743 ***	57 ***	M	M	M
23	621 **	36 ***	M	M	M	M	M	M	616 **	58 ***	M	M	M

ERP values at Pz unless shown. Cases are entered in the table in increasing MRI score as given in Table I.

# = value measured in channel Fz; + = value measured in channel Cz; M = low amplitude, multiple peaks, impossible to identify components; a = cursored and measured with filter at 10 Hz cut-off to eliminate intrusive alpha activity; b = significant interchannel latency differences: Case 3—Fz-Cz (***), Case 6—Fz-Cz and Fz-Pz (***), Case 17—Cz-Pz (***) both modalities; c = abnormal amplitude 0.8 μV (***); ** $P < 0.01$, *** $P < 0.001$ compared with age-matched control values. Values in round brackets were significantly different from the age-matched control values but not from the regression line norms, whereas the reverse was the case for values in square brackets. None of the values in brackets was counted as being abnormal.

was sufficient to make the interelectrode P3 latency differences between channels Fz and Cz and Fz and Pz highly significant ($P < 0.001$), whereas this was not the case preceding correction for remaining eye movement artefact. A high error rate for target responses led to re-averaging from single trials for 10 cases. After excluding trials containing eye movements as well as those on which the patient did not respond, there were insufficient sweeps to produce a recognizable target waveform for 2 patients (Cases 18, 19). Otherwise the mean number of sweeps in the averages for the target stimulus in the auditory task was 55 (range 17–75), including a mean of 2.2 trials associated with incorrect behavioural responses (range 0–16). Corresponding figures for the nontarget auditory stimulus were 57 (range 33–73) and 0.4 (range 0–3) and for the frequent auditory stimulus 320 (range 193–487) and 0.8 (range 0–4). In the visual task the mean number of sweeps in the averages for the target stimulus was 63 (range 27–75), including a mean of 0.3 trials associated with incorrect behavioural responses (range 0–3). Corresponding values for the nontarget visual stimulus were 62 (range 30–75) and 0.2 (range 0–1) and for the visual frequent stimulus 317 (range 175–383) and 0.6 (range 0–8). There were significantly more sweeps in the patient averages for frequent stimuli in both modalities compared with controls and for responses to visual nontarget stimuli. There were no differences between the two groups in terms of the number of trials associated with incorrect behavioural responses contained within the averages. The differences between the two groups are due to the inclusion of 7 control subjects for whom 40 artefact-free target trials was the acceptance criterion rather than 75 artefact-free target trials or a total of 600 stimulus presentations used for all other subjects.

Two patients (Cases 22, 23) had comparatively low amplitude waveforms with multiple small peaks and no components that could be identified confidently in any of the conditions tested. The waveforms for one of these patients are shown in fig. 4. A further patient (Case 21) had low amplitude waveforms for the auditory target and nontarget stimuli and was not tested in the visual modality because of poor acuity. The waveforms obtained from the auditory task for one subject were obscured by high amplitude alpha activity

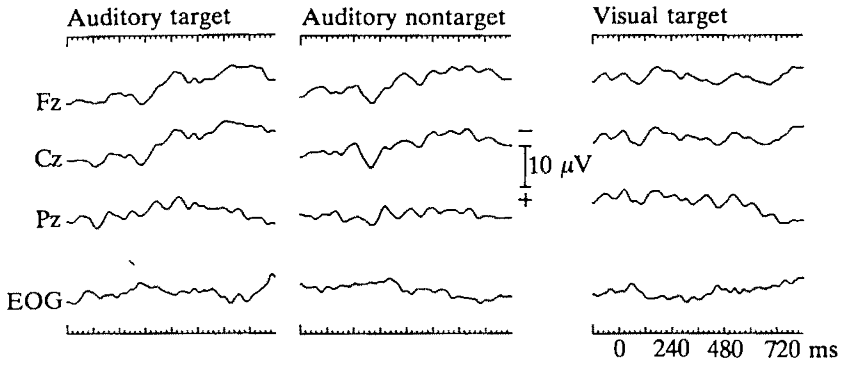

FIG. 4. *Case 22*. Example of low amplitude responses with unidentifiable components.

(Case 2). This activity was removed by filtering the waveforms at 10 Hz cut-off and comparing the latencies of resultant peaks with normal limits obtained from similar filtering of the control group's responses. Apart from these cases, the early components evoked by both auditory and visual stimuli (N1, P2 and P160, N200, P250, respectively) were generally well-defined and of normal latency and amplitude. The only exceptions to this were Cases 15 (delayed P2 at Fz) and 5 (delayed P250 at Pz) as well as 4 cases who had poorly-defined P2 components (Cases 5, 8, 9, 14). Of these 5 patients only Case 8 did not have an abnormality in the later components.

The majority of abnormalities occurred for N2 and P3 latencies and SW amplitude. In spite of the apparent reduction of N2 amplitude for the patient waveforms shown in figs 1 and 2, none of the individual patients had an abnormally small N2 in either modality. There was only one instance of an abnormal P3 amplitude (Case 11). Table 4 gives N2 and P3 latencies and SW amplitudes from the target and nontarget waveforms of the auditory tasks and the target waveforms of the visual task for each patient. Cases are entered in the table from lowest to highest MRI score to aid assessment of any relationship between MRI and ERP abnormalities. The measurements are for the Pz electrode unless indicated. In general, a component that was abnormal at Pz was also abnormal at one or both of the other midline electrodes. Fig. 5 illustrates a case with abnormal P3 latencies in each of the midline electrodes and fig. 6 shows a patient with an abnormal P3 latency in the Pz channel only. In a few cases, components were normal at Pz but abnormal at another electrode and these instances are indicated in the table. For 3 cases (3, 6, 17) the absolute latencies and amplitudes were normal but the interchannel P3 latency differences were outside the normal range. For 2 of these cases (3, 17) this was the only abnormality found. For Case 3 the interchannel difference was prolonged for the visual modality only, whereas for Case 17 the difference was abnormal in both modalities.

A total of 8 patients had abnormal latencies or amplitudes (Cases 5, 6, 9, 11, 14, 15, 18, 19) plus 2 with interchannel differences alone (Cases 3, 17). A further 3 had

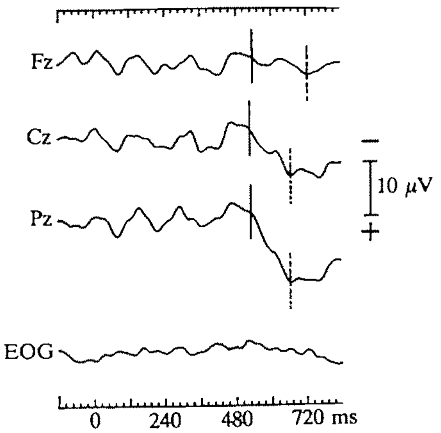

FIG. 5. *Case 9.* Recordings showing a significantly delayed P3 component to visual target stimuli. The solid vertical lines indicate the upper limits of normal for age-matched control data and the dashed vertical lines show the points at which P3 latency was measured for this subject.

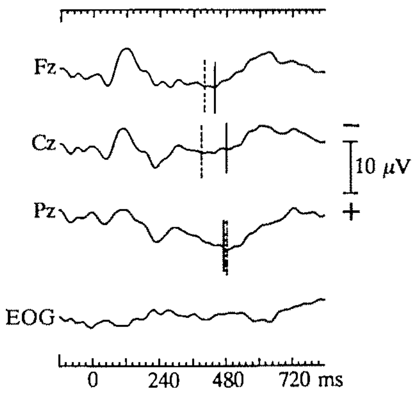

FIG. 6. *Case 15.* Example of a significantly delayed P3 latency to auditory targets at one electrode site only. Solid and dashed vertical lines have the same meaning as for fig. 5. Note the degraded nature of the waveforms following the P2 component.

completely unidentifiable waveforms (Cases 21, 22, 23). Of these 13 patients, 9 also had abnormal RT measures. RT performance alone was abnormal in Cases 2 and 16 (although the slow-wave amplitude for the visual task for Case 2 was abnormal on one criterion but not the other). Patients' waveforms tended to contain either clearly-defined components of normal latency or low amplitude, broadened components which were

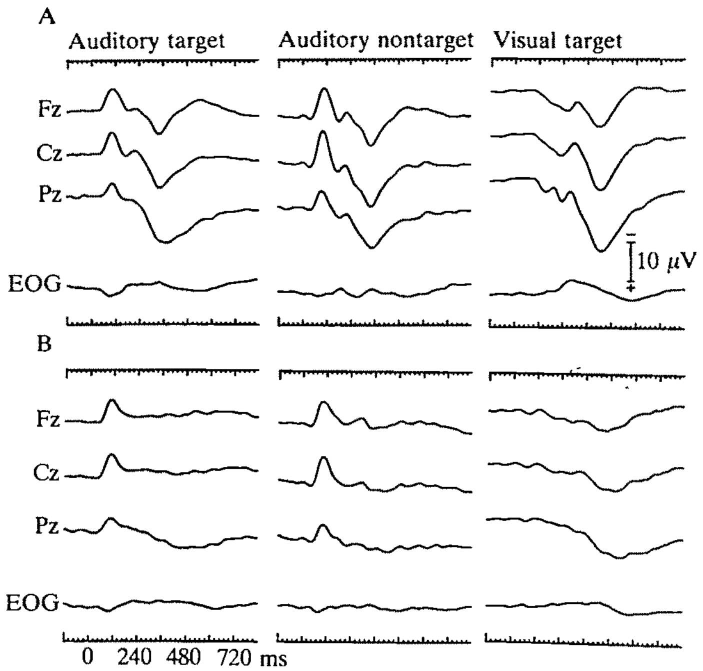

FIG. 7. Group average waveforms for MS patients with normal ERP measures (A) and those with abnormal measures (B). Note the close similarity between waveforms for the normal group and those for the control subjects in fig. 1. Note also the degraded responses for the abnormal group and the retained auditory N1 component for these subjects.

often hard to identify. Thus where Table 4 indicates values for abnormal latency or amplitude these measures were usually taken from poorly-defined waveforms (e.g., fig. 6). This was more often the case for responses in the auditory rather than the visual task (e.g., Case 9 in fig. 5 has a clearly-defined but delayed P3). Fig. 7 reinforces this point by comparing average waveforms for patients having normal component measures with those for patients having abnormal measures.

Correlations between clinical, MRI measures, tests of cognitive function and ERPs

A comparison between the results of electrophysiological tests of sensory function and ERPs for the patients described here is given in Table 5 in which cases are ordered from low to high MRI score. There was a high incidence of abnormality for the tests of sensory function with only 3 patients having no abnormal results (Cases 4, 7, 16). These 3 patients also had normal ERPs.

The patient with isolated optic neuritis (Case 10) had entirely normal ERPs. Of the 23 patients with MS, those with abnormal ERPs had both a longer duration of disease (12.5 yrs vs 7.0 yrs; independent $t = 2.17$, $P < 0.05$) and a higher mean score on

TABLE 5. COMPARISON OF RESULTS ON TESTS OF SENSORY AND COGNITIVE FUNCTION FOR PATIENTS ENTERED INTO THE TABLE IN INCREASING ORDER OF MRI SCORE AS TAKEN FROM TABLE 1

Case no.	*MRI score*	*Sensory*			*Cognitive*	
		BAEP	*VEP*	*SEP*	*Aud.*	*Vis.*
10	0	N	A	N	N	N
12	3	N	A	N	N	N
7	3	N	N	N	N	N
6	4	–	A	A	N	A
1	6	N	N	A	N	N
17	9	–	A	A	A	A
2	14	N	A	N	N	N
24	17	–	A	N	N	N
16	18	N	N	N	N	N
4	20	–	N	N	N	N
8	23	N	A	N	N	N
15	24	N	A	–	A	N
20	25	–	A	–	N	N
14	28	–	–	–	A	A
3	28	–	A	A	N	A
21	33	A	A	A	A	–
13	33	A	A	A	N	N
5	35	–	A	–	A	N
18	36	A	A	A	A	–
9	37	–	A	–	A	A
11	39	–	–	–	A	A
19	40	–	A	–	–	A
22	46	A	A	A	A	A
23	54	–	A	–	A	A

BAEP = brainstem auditory-evoked potential; VEP = visual-evoked potential; SEP = somatosensory-evoked potential; Aud. = auditory modality; Vis. = visual modality; N = normal test; A = abnormal test; – = test not done or impossible to evaluate (cognitive test Cases 18 and 19).

the Kurtzke disability scale (4.9 vs 2.7; independent t = 2.19, $P < 0.05$). Seven of the 10 patients with a history of depression had abnormal ERPs (5 had latency abnormalities and 2 had unmeasurable waveforms). With respect to the 18 MS patients in whom IQ and memory deficits were assessed, 2 of the 4 patients with an isolated deficit on the test of visual memory had abnormal ERPs (Cases 9, 14) as did 4 of the 6 patients with intellectual deterioration (Cases 11, 17, 19, 23). Two of these 4 had abnormal scores on all 3 tests of cognitive function (Cases 11, 17). Thus 6 patients

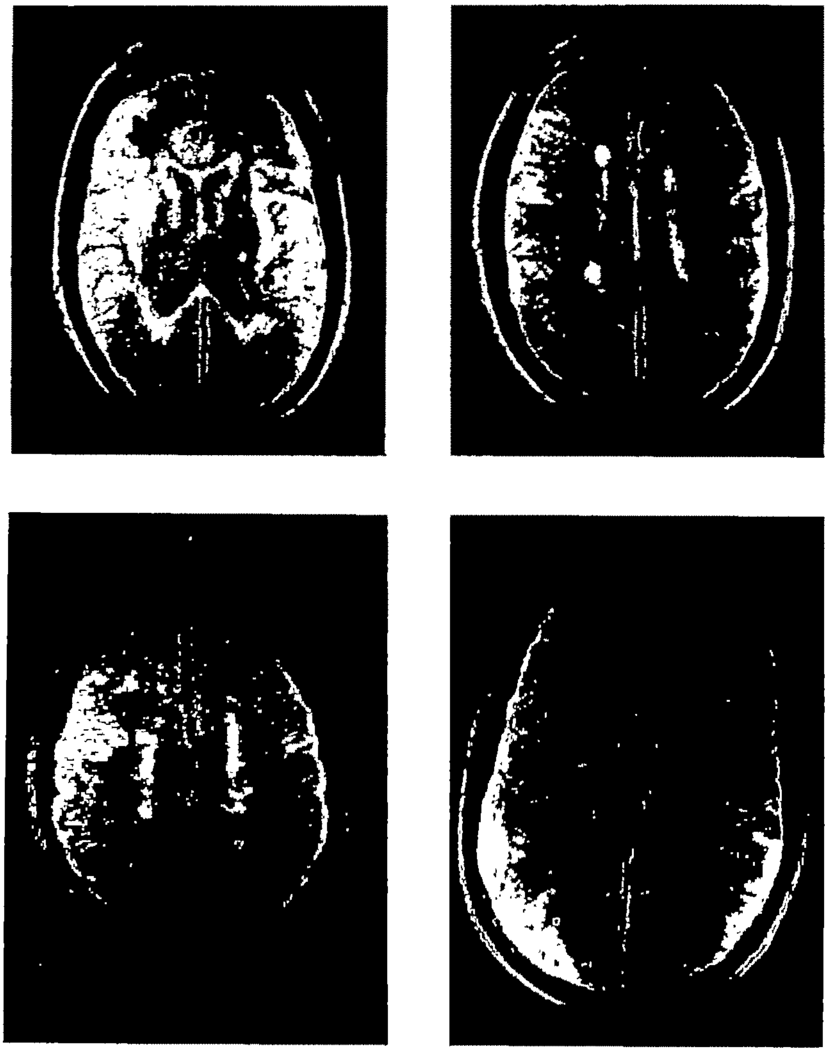

FIG. 8. MRI scans from 4 patients. *Top*: 2 cases with a high MRI score and abnormal ERPs (left = *Case 9* from fig. 5; right = *Case 15* from fig. 6. *Bottom left* shows a scan for a patient with a high MRI score and normal ERPs (*Case 20*) and *bottom right* shows a scan for a patient with a low MRI score and normal ERPs (*Case 1*). MRI scores are given in Table 1.

were abnormal on both tests and 4 patients with abnormal IQ or memory scores had normal ERPs. In addition, 3 patients were normal on both tests (Cases 1, 7, 16) and 5 cases with normal IQ and memory scores had abnormal ERPs (Cases 5, 6, 15, 18, 22). All patients, apart from Cases 11 and 23, achieved a normal score on the tests of current mental state administered at the time of ERP testing. Both of these cases had abnormal ERPs. The 13 cases of MS with abnormal ERPs had an MRI score almost twice that of the 10 cases with normal ERPs (31.8 vs 16.2; independent $t = 3.04$, $P < 0.01$). Although the group with abnormal ERPs had a lower proportion of lesions in the periventricular regions than those with normal ERPs, the difference was not significant (62.8% vs 70.8%; independent $t = 1.72$, $P < 0.1$). Fig. 8 shows the MRI brain scans for some of the patients whose ERPs are illustrated elsewhere in the paper. They show 2 patients with a high MRI score and abnormal ERPs (Case 9 from fig. 5 and Case 15 from fig. 6), a patient with a high MRI score and normal ERPs (Case 20) and a patient with a low MRI score and normal ERPs (Case 1).

DISCUSSION

We have shown a high incidence of abnormal cognitive ERPs in a group of MS patients (13/23, 57%). The low incidence of abnormality for the early components in responses to auditory and visual stimuli (N1, P2 and P160, N200, P250) indicates that early sensory processing is normal in the majority of these patients but that subsequent cognitive processes such as stimulus evaluation are abnormal. This is reinforced to a certain extent by the entirely normal appearance of the N1 component in the averages to auditory stimuli for those patients with abnormal ERP measures (fig. 7). These sensory-related 'early' components of the ERPs for these patients were normal even though there was a high incidence of abnormality on evoked potential tests of sensory function (Table 5).

Of the 18 MS patients in whom intellectual deterioration and memory function were assessed, 5 of 8 with normal IQ and memory had abnormal ERPs and 4 of 10 with abnormal IQ and memory had normal ERPs. Only 2 of our MS cases had abnormal scores on tests of current awareness (IMC or MMS), very often the only test used to assess cognitive function in studies of ERPs in clinical populations. Patients with abnormal ERPs had MRI scores twice those of patients with normal ERPs.

Cognitive ERPs have been used previously in investigating the electrophysiological manifestations of Alzheimer's disease (Goodin *et al.*, 1978*b*; Syndulko *et al.*, 1982; Pfefferbaum *et al.*, 1984*b*; St Clair *et al.*, 1985; Gordon *et al.*, 1986; Neshige *et al.*, 1988) and the 'subcortical' dementias associated with Parkinson's disease and Huntington's disease (Hansch *et al.*, 1982; Lawson *et al.*, 1984; Goodin and Aminoff, 1986; Hömberg *et al.*, 1986). In the study of Goodin *et al.* (1978*b*) P3 delays were found in 80% of the demented patients, who had a mean MMS score of 20.3 out of 30, and in only one nondemented case. This high proportion of ERP abnormality was also found by Syndulko *et al.* (1982) with 10 out of 12 demented patients having abnormal P3 latencies and by Gordon *et al.* (1986), although the latter authors felt that P3 delay was not necessarily specific to dementia. Pfefferbaum *et al.* (1984*b*) also found P3 latency and amplitude changes to be nonspecific for dementia and obtained a much lower proportion of abnormalities than other authors. Our MS patients, however, had minor cognitive changes in comparison with those described above with all but 2 having normal scores in the current awareness tests. The high proportion of abnormal ERPs for the oddball paradigm given to our MS patients (13/23) suggests that processes involved in stimulus evaluation are affected by demyelination. Of particular interest is that 5 patients with abnormal ERPs had no deficit on tests of intellectual deterioration and memory. This suggests that the ERP may be a potentially useful technique in demonstrating electrophysiological abnormalities in the absence of clinically demonstrable deficits. Whether more detailed cognitive testing such as that described by Callanan *et al.* (1989) would reveal abnormalities in these patients remains to be seen.

Apart from patients for whom no ERP components could be detected, the majority of abnormalities occurred for N2 and P3 latency with no instance of an abnormal N2 amplitude and only one occurrence of an abnormal P3 amplitude. This is somewhat surprising given the apparent reduction in N2 amplitude observed in the patient waveforms illustrated in figs 1 and 2. However, the variability of component amplitude in the normal population is high (*see* Table 3) resulting in confidence limits which often allow the inclusion of both negative and positive amplitudes and which are rarely exceeded.

Abnormal performance scores alone (mean RT and % hits) presumably reflect difficulties in some or all of sensory processing, stimulus evaluation or response execution. The addition of ERP measures provides information which helps to distinguish which of these processes is deficient in any particular patient. It is notable that 9 of the 11 patients with abnormal performance scores also had abnormal ERPs. The fact that the N1 component to auditory stimuli and the P160 and N200 to visual stimuli were normal in every case suggests that sensory processing is not the problem, despite the high incidence of abnormality on electrophysiological tests of primary nervous function (Table 5). The relationship between prolonged RTs, abnormal performance and greater disability suggests that deterioration in the motor functions of the nervous system may be affecting response execution. Indeed, 5 of 7 patients with abnormally long RTs had Kurtzke disability scores of 6 or higher. However, these 7 cases also had delayed (4) or absent (3) P3 potentials suggesting that difficulties in stimulus evaluation have at least contributed to the prolonged RTs. Thus it appears that cognitive processes required to perform these oddball tasks as well as motor function are being affected by demyelination. Grant *et al.* (1984) reported a high incidence of subclinical short-term memory deficits in patients with a short history of MS. Although a relationship between memory processes and P3 recorded in the oddball paradigm has been suggested (Donchin, 1981), an ERP test designed specifically to assess short-term memory deficits (e.g., Starr and Barrett, 1987) might produce a higher incidence of abnormality in MS patients than found here.

As well as greater disability, abnormal ERPs were also associated with longer disease duration and a higher MRI score indicating (in general) a more widespread disease process. Patients with abnormalities on the tests of intellectual deterioration and memory had average scan scores of 28.8 compared with 21.5 for those with normal test scores ($P > 0.05$). Huber *et al.* (1987) also found no correlation between MRI lesion score and cognitive function using similar although not identical cognitive tests. They did find an association between increasing physical disability and cognitive abnormalities in their study, a trend which was also observed in our investigation. It is of interest that the distribution of lesions seen in the MRI scans of MS patients with normal and abnormal ERPs in our study was not significantly different, with each group having a similar percentage lesion score in the periventricular areas and in the hemispheres. However, in interpreting the MRI findings it must be appreciated that a lesion observed in one scan may not be present in a subsequent scan of the same patient. Lesions may also change in size, and of course many remain invisible to MRI so that this imaging technique can only give an approximate guide to the extent of white matter disease.

With regard to correlations between affective illness and cognitive ERPs, Pfefferbaum (1986) reported variable reductions in P3 amplitude in depressed patients, Gordon *et al.* (1986) reported a low (12%) incidence of increased P3 latency in depressed patients and Blackwood *et al.* (1987) found no latency changes but a reduced P3 amplitude which returned to normal after treatment. Seven of our 10 patients with a history of depression had abnormal ERPs, but the abnormalities were principally latency prolongation (5 cases) with 2 cases having unmeasurable waveforms. Furthermore, none of the patients was being treated for depression at the time of the recording. The high MRI score of most of these 7 'depressed' patients reflects more extensive disease which could of itself be responsible for the ERP abnormality rather than depression per se.

The apparent bimodal distribution of RTs and ERP waveform morphology in these patients suggests that any cognitive dysfunction that is being measured by the oddball task is of an all-or-none rather than continuously progressive nature. Sequential studies of patients with dementing illness have shown changes in P3 latency paralleling improvement or deterioration in clinical condition (Goodin *et al.*, 1983; St Clair *et al.*, 1988). Clearly it would be informative to perform such studies on patients in the early stages of MS in order to establish how the decline in cognitive function compares with the progressive nature of the dementias in Alzheimer's, Parkinson's and Huntington's diseases.

Although there is evidence that a P3 component in the oddball task is generated in the human hippocampus and amygdala (Halgren *et al.*, 1980), it is likely that the component recorded from the scalp includes contributions from a number of generator areas, some of which may be closer to the cortical surface (Wood *et al.*, 1980). It is clear from this study that lesions of the cerebral white matter have an influence on the generation of scalp-recorded cognitive ERPs. However, a lesion site identified from an MRI scan need not itself be responsible for generating an ERP but may represent a block in fibres connecting areas which are so responsible. Of particular interest with regard to the generation of P3 are the 3 cases with abnormal interelectrode latency differences. Such differences were small and consistent in the normal control group. These latency differences between components recorded at midline electrodes are difficult to explain in terms of changes to a deep generator such as the hippocampus; they more likely represent selective changes to cortically-generated 'P3' components.

We have provided evidence that ERPs recorded using the oddball paradigm may be a useful method of measuring aspects of cognitive function in MS that are not necessarily detected by standard tests of intellectual deterioration and memory and thus ERPs may have a complementary role to play in the cognitive assessment of patients with MS. Although ERP abnormalities tended to be related to more extensive demyelination, as shown by MRI, and greater disability, the exceptions to this rule encourage wider study of ERPs in nondisabled patients with MS and patients presenting with early manifestations such as optic neuritis. From there it will be possible to learn whether cognitive ERPs have any role in diagnosis and to measure how early the electrophysiological changes begin in the course of MS.

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BOOK REVIEWS

Yearbook of Neurology and Neurosurgery 1989. Edited by R. N. DeJong, R. D. Currier and R. M. Crowell. 1989. Pp. 438. London: Wolfe Medical. Price £32.00.

Even the most industrious and conscientious of clinicians will have to concede that it is increasingly difficult, if not frankly impossible, to keep up with the ever burgeoning neurological literature. Apart from our own particular and often limited field of special interest, most of us will have to confess that we scan regularly only a few journals, glancing at titles of papers, occasionally reading a summary, perhaps paying attention to book reviews and, as we grow older, the obituaries.

The most agreeable way to assuage this guilt is to have the justifiably celebrated *Yearbook of Neurology and Neurosurgery* near one's favourite chair. The onerous task of critically surveying over 700 journals and somehow reducing the vast breadth of coverage to a compact and readable format is in itself a spectacular achievement, but it is the distinctive quality of editorial comment—scholarly, critical yet personal, relaxed and at times amusing—which makes the Yearbook obligatory reading. For the few who may not have relished these exemplary editorial skills, a few examples from the current volume can be quoted. Thus, commenting on a complex randomized prospective study to determine whether a subtherapeutic dose of anticonvulsant should be increased in well stabilized epileptics, an editor comments: 'The answer is No, a conclusion that is not really surprising.' On the vexed question of the value of early anticoagulation in cardioembolic stroke an editor wryly remarks: 'We were better off when it took a day or so to obtain a CT scan and when our methods of giving Heparin were not as efficient. Why don't we wait three or four days after the embolic stroke, repeat the CT scan, then if we think that the patient should be heparinised for the prevention of further emboli, do it? For that matter, why not forget the Heparin and start with Warfarin?' It is also reassuring to read frank confessions about previous judgements: 'It is sad to hear that our original optimism was misplaced.' On occasions the editor's enthusiasm for a particular topic is so evident that he cannot resist adding his personal recommendations for further reading. This chatty discursive style creates the atmosphere at a personal tutorial with a wise and omniscient teacher and could only be achieved from prodigious editorial ability, energy and attention to detail. Going strong since 1902, all clinicians will welcome another successful Yearbook with pleasure and gratitude.

GERALD STERN

Neurological Examination in Clinical Practice. By Edwin R. Bickerstaff and John A. Spillane. Fifth edition. 1989. Pp. 371. Oxford: Blackwell. Price £39.50.

In the 25 years since the first edition of this classic text, there have been rapid and far-reaching changes in the practice of clinical neurology. These have in no way diminished the necessity to present a traditional clinical methodology which has stood the test of time.

Those who know this book from early editions will recognize the skill and care with which the neurological examination and clinical history are detailed. It is an excellent and appropriate text for neurologists in training and for physicians who may be responsible for the evaluation of acute and subacute neurological problems. At this level the tendency to didacticism and at times dogmatism can be readily accepted as an essential part of the approach to neurological discipline. There is a wealth of accurate descriptive detail and this book is at its best in defining and interpreting the relevance of clinical signs in clinical neurology and their anatomical substrate.

The authors would be the first to agree that in the changing field of neurological investigation there is a constant need for flexibility and for frequent reappraisal of current and in some instances archaic investigations, in the light of new developments. This applies most pertinently to the precise relevance of myelography and to the whole field of neuroimaging. It seems inevitable that future editions will deal with the role of special investigations only in a general sense and that accelerating advances in neurotechnology will be displaced into the more specialized field served by the monograph.

There is an abundance of good sense and instruction in this book which represents the best in the application of clinical neurological examination and technique to everyday problems posed by neurological disease. The authors are to be congratulated on maintaining the high standard that is traditional and necessary to an understanding of the practice of clinical neurology; carefully written in the authors' inimitable style, it is a valuable instructional text with a balanced historical perspective.

J. R. Heron

Cerebrovascular Disease. Sixteenth Research (Princeton) Conference. Edited by Myon R. Ginsberg and W. Dalton Dietrich. 1989. Pp. 453. New York: Raven Press. Price $56.50.

The Sixteenth Princeton Conference on cerebrovascular disease took place in March 1988. Although it is customary to decry the delay in publication in a rapidly advancing research field, the Princeton Conference reports are somewhat of an exception. Thus although some data have been superceded, the insights of the collaborators revealed in the verbatim discussion sessions are worth reading, however late they appear. The best value of any small conference is the discussion, both formal and informal, and it is the success of the Princeton reports that they gave a real flavour of the discussions that take place.

This issue covers some highly important topics in the research growth concerning cerebral ischaemia from excitotoxins, thromboplastin activator, hyperglycaemia, oxygen radicals, the blood-brain barrier, lipids, and platelets, to recovery from stroke and multi-infarct dementia. Although most authors press the case of their own magic bullet approach, it emerges that interdisciplinary thinking will be needed and treatment may have to be something of a cocktail to block all potentially cytopathic and noncytopathic neurotoxic effects provoked by ischaemia.

There is an interesting section on multi-infarct dementia and on Binswanger's demyelination, but this volume will be most attractive to those involved in the pathophysiology of cerebral ischaemia and its recovery. Some cynics have suggested that everything works in animal models as a neuroprotective agent, but nothing works in man. The ischaemic models remain the only test bed for neuroprotection currently available, however, though metabolic studies in man are coming to represent an intermediate step between the laboratory and the costly multicentre clinical trial. The next few years will see a further rash of such trials—they will have had their origins in discussions like those at the Princeton Conference, which gives the proceedings a bit of the flavour of a 'trailer'.

Drs Barnett and Caplan at the meeting kept the group's feet on the ground by asking 'country doctor' questions. The country doctor will read in this book about tomorrow's clinical trials and hopefully the day after tomorrow's treatment. It is so expensive, however, that he will probably have to live in the same village as someone who has reviewed the book and from whom he can borrow it.

M. J. G. Harrison

The Management of Acute Stroke. Edited by C. M. C. Allen, M. J. G. Harrison and D. T. Wade. 1988. Pp. 215. Tunbridge Wells, Kent: Castle House. Price £35.00.

This book is written by three neurologists and is aimed at physicians who look after stroke patients; in the British context at least, these are not neurologists but geriatricians, general physicians, and general practitioners. It is not a book for those doing active research into stroke, but for those who are seeing stroke patients on the ward or at home and who want to know about state-of-the-art stroke care which is exactly what this book will give them. Indeed, knowing too much about stroke could cause some minor irritations in a reader; for example, it is rather an exaggeration to say that 25% of cerebral infarct patients are in atrial fibrillation, fibrinogen is not mentioned as a risk factor for cerebral infarction, and measuring the blood glucose is not mentioned in the investigation of acute stroke. However, unusually for a book like this, there are good chapters on rehabilitation as well as the more conventional medical and surgical treatments for cerebrovascular disease. The treatment recommendations are entirely reasonable although there seems to be an implication that patients do not need aspirin as an antithrombotic drug after carotid endar terectomy, a view with which I personally would not agree. The references are well chosen and up-to-date, the illustrations and figures are excellent, and the book looks good. It is not too big and I think there are no comparable up-to-date British books on the subject. I would certainly recommend it to anyone who looks after stroke patients.

CHARLES WARLOW

Thought Without Language. Edited by L. Weiskrantz. Fyssen Foundation Symposium Series No. 2. 1988. Pp. 533. Oxford: Clarendon Press. Price £30.00 (paperback), £60.00 (hardback).

This is an unusual, delightful and invaluable book: unusual because it represents a unique cross-section of the fields relevant to its title; delightful because of the diversity and unexpectedness of some of the findings reported; and invaluable because of the range and quantity of clinical and basic scientific data which it contains. The range of techniques used to acquire the data could not be greater, from the most sophisticated surgical and neuropsychological techniques in animals and man to the feeding of dogs in a field and the observation of babies with their mothers.

The central problem addressed is the nature of, and extent to which cognitive processing occurs in the absence of language. The outstanding success of the book derives from the way in which it was put together. A symposium was organized under the auspices of the Fyssen Foundation and a decision made at the outset that the discussion would be organized around six central problems rather than ordered according to the usual disciplines within which the contributors work—human development, experimental neuropsychology, clinical psychology and clinical neurology. The papers were circulated in advance and were afterwards revised in the light of the taped discussions and subsequent written replies to particular questions. There is as a result a high degree of integration of the chapters, something which is remarkable both for its rarity in publications arising out of symposia and for the fact that for many of the contributors this was their first opportunity to discuss in depth their own work with others with quite different backgrounds. Much of the credit must go to the editor, Professor Weiskrantz, who has provided an introduction to the volume as a whole and to each section. These are important since no reader—least of all the practising neurologist—will have the critical range to comprehend the technical details in all the fields represented, and to assign due weight to the conclusions from them.

The book is divided into 7 sections, each of the first 6 of which having 3 chapters. The first section deals with the role of instruction in the development of cognition, the evidence being derived from an analysis of child development (Butterworth and Grover; Mounoud) and the results of attempts to train chimpanzees in language and problem solving (Premack). Section B deals with the categorization of percepts, making particular use of research on vision both in normal individuals and in patients with prosopagnosia (Young; Sergent). The relationship of stimulus generalization to the acquisition of categories is explored in the pigeon (Pearce) and the common ground and differences between the mechanisms involved in animals and man are discussed.

The ontogeny of perceptual and causal knowledge in man is explored in Section C (Spelke; Leslie; Cohen). The various forms of dissociation produced by cerebral lesions between the capacity to discriminate and learn and the knowledge that patients have of the operation of these capacities are discussed in Section D. The paper by Schacter *et al.*, dealing as it does with amnesia, blindsight, prosopagnosia, dyslexia, dysphasia and hemineglect, is of considerable practical interest to the neurologist. It leads on to the development of a model of implicit/explicit dissociation. An account by Horn of work on imprinting in pigeons shows, as the editor points out, a growing convergence between the study of dissociations in experimental animals between multiple types of memory systems and associations between implicit and explicit processes in man, and offers exciting potential for elucidating the neural mechanisms underlying the dissociations. Some of the logical questions concerning intentionality and beliefs in animals are carefully dissected by Dickinson, who adduces experimental evidence to help decisions at critical points in the argument.

Section E deals with the mechanisms underlying the acquisition of knowledge about shape and space and memory of them, and how they are used in decision making in infant and adult humans and in animals (Diamond; Thinus-Blanc; Bresard). Section F deals with the interaction between thought and language on the basis of evidence derived from a study of split brain patients (Gazzaniga), aphasics (Kertesz) and patients with various forms of spatial misrepresentation (Bisiach).

Finally, Section G is a moving personal account by a gifted university mathematician of what it means to be profoundly dyslexic. The story (transcribed by others from an oral presentation, so severe is his disability) is not only interesting on a personal level, but for the glimpses it gives into his nonverbal ways of thinking in relation to mathematical research.

Several general points emerged which are of particular neurological interest. The first is that the application of the methods of experimental psychology to man is leading to new insights into cerebral processing and cognitive function. Secondly, many of the clinical syndromes are more variable in the detail of their manifestations than is commonly realized. Failure to appreciate this point has been the source of some of the controversies, for example in relation to blindsight. Thirdly, while the application of new methods is leading to a better understanding of focal specialization of function in the cerebrum they are also showing that 'localization' is often more complex than is generally supposed. Gazzaniga from his studies of split brain patients argues convincingly that the notion that the left hemisphere is concerned with the control of verbal function and the right with nonverbal function, should be replaced by a modular account in which the modules are spread throughout and across various loci. An interesting suggestion deriving from the split brain data was that while certain nonverbal inputs can be processed by either hemisphere, the right deals with them more speedily and more effectively because it is not burdened with ineffective and unnecessary analytical efforts.

As to the basic question as to whether thought can occur without language, the answers are admirably summarized by the editor in a final chapter. The existence of cognitive capabilities in the absence of language is clearly established. As to whether 'thought' or 'thinking' can occur in the absence of language is more difficult. Professor Weiskrantz makes the helpful suggestion that it is useful to consider the question in the light of the way the word 'think' is used in everyday speech—to think *of*, to think ***through***, to think ***in***. There is abundant evidence that things can be thought *of* in the absence of language: the prelinguistic infant can understand where a hidden object is and the chimpanzee can have an abstract understanding of ratio. To think ***through*** in the sense of putting separate items of information together or to consider implications, is evidenced by animals putting separate items of spatial information together to yield a direct route, champanzees adding two ratios of physically unlike items to match a third quantity, again physically different, and some aphasic patients demonstrating nonverbal logical sequencing. It is still unclear whether it is possible effectively to think *in* a nonverbal way. That thinking in words is usual, however, does not carry the implication that there can be no other medium.

One of the strengths of this remarkable book is the critical approach the authors adopt to their own work, especially when it comes to model building and generalizing the findings from the specific circumstances in which the observations were made. Clear indications as to fruitful lines of further research abound. Its usefulness to neurologists and neuropsychologists, both experimental and clinical, is obvious. It is also I think an ideal book to put in the way of the young scientist or physician who is contemplating a career in this most challenging field of study. I certainly shall.

W. I. McDONALD

Agnosia and Apraxia. Selected papers of Liepmann, Lange and Pötzl. Edited by Jason Brown. 1988. Pp. 329. London: Lawrence Erlbaum. No price stated.

This collection of selected translations of the papers by Liepmann, Lange and Pötzl is introduced briefly by Jason Brown.

I enjoyed reading the translation of Liepmann's review of apraxia because it was very close to my own unpublished translation undertaken in collaboration with my father. Liepmann is difficult to read in German and also in this translation, which tries to reproduce the original faithfully. Not only are the sentences lengthy, but these articles demonstrate the idiosyncratic writing style of that era, such as the use of the third person by the author when referring to himself. For instance, let the reader try to make sense of the second paragraph!

Liepmann in his introduction to his review, gives credit to Steinthal, the linguist who first used the term 'apraxia' and he discusses Nothnegel's psychic paralysis and Meynert's 'motor asymbolia', as similar concepts. The most interesting aspect of Liepmann's essay is his attempt to grapple with the relationship of physiological mechanisms versus psychological ones. His theory of kinetic engrams as distinct from the ideational outline of movement (connected to the image of outcome) is quite modern and some of it has been supported by physiological evidence. He defines the idea of movement and its target as an extrakinetic space-time outline, and postulates that its neural mechanism is mostly visual. He elaborates the relationship of the kinetic engrams and the 'motion outline', or idea of motion, and emphasizes that the distinction between these two processes is essentially didactic and, at best, an over-simplification. At the two extremes of Liepmann's apraxia spectrum are the loss of kinetic engrams and the loss of ideational outline of movement. The connection between them may be deficient, forming a third variety called ideomotor apraxia. In addition to the three types of apraxia, the kinetic, ideomotor and ideational, Liepmann also classified the types of movement into eight groups, such as those with 'conventional meaning' (now called 'iconic movements'), object manipulations, transitive movements without the object present, imitations of arbitrary motions (presumably he meant nonsense movements), motions without an object which have a physical effect (such as whistling and panting), reflex motions (such as scratching oneself, touching the face, twirling a moustache), and elementary body-part motions without objects. Some of these have resurfaced in subsequent classifications without sufficient credit being given to Liepmann. He also provided a detailed error analysis and classifies these errors as amorphous motions, coarsened and mutilated movements, exchanged motions, perseveration of earlier movements, completely unrelated motion and the omission of motion. He distinguished errors that occur in sequential movements.

It would have been useful to have had some comments on the translated review, for instance on Liepmann's classification of motor apraxia. It could be pointed out that the diagnosis of limb kinetic apraxia is rarely, if ever, used because of the difficulty with its separation from mild paresis. Liepmann's first patient was far from typical as his severe apraxia was restricted to the right hand. It would have been helpful to have some comments on the controversy of the definition of ideational apraxia, as Liepmann's definition of ideational apraxia as an apraxia of complex movements is not followed by the majority of researchers in this field. The actual translated paper is not referenced. The illustrations, on the other hand, are well reproduced from Liepmann's articles and it is very helpful to have them all collected in one review.

Lange's review of agnosia and apraxia is also heavy reading. It is really a book-sized, at times rambling, anecdotal review of the literature on agnosia and apraxia. Unfortunately the translators do not provide the original reference.

Lange makes a case for the unified nature of identification and action, and this is an important concept because in the modern literature they are almost always dealt with separately. The research on agnosia developed from experimental physiology rather than from clinical studies. Lange reviews the psychophysical experiments that are relevant to visual agnosia. Some of these, such as the study of chronaxy, are not in use any more but the optical disorders of perception were studied in a surprisingly sophisticated fashion in the early decades of this century. Interesting are the tachistoscope experiments in the case of Stein, who not only had agnosia and many interesting optical deficits but also the amnestic syndrome.

Lange tends to go from one author to the next without indicating where the reference comes from, assuming perfect familiarity with the literature on the part of the reader. The original observations of Charcot and Wilbrand have been expanded by several generations of investigators, such as Munk, Poppelreuter, von Stauffenberg, Balint, Gelb, Goldstein, Bielschowsky, Hartman, Kleist, Uchthoff and Pötzl, and each of these is quoted, criticized and praised in great profusion. Charcot's type of psychic blindness is what we now would call prosopagnosia but that was of course before prosopagnosia was described. Much of this extensive body of descriptive work seems to be lost to the modern cognitive psychologists who are applying processing diagrams to the phenomena of visual recognition deficits. Lange's description of Poppelreuter's experiments is of great interest. His postoperative, posttraumatic patients are placed in context of severity and evolution after the acute trauma. Poppelreuter is praised by Lange because he carried out 'unprejudiced' examination of unselected patients with damage to the occipital region. In this report, Poppelreuter was indeed the first modern neuropsychologist in the field of visual agnosia.

Lange also reproduces in detail several case illustrations including one of Poppelreuter's and one of Gelb and Goldstein's, the famous Schn. The insights of the Schn. case are greeted with scepticism, although they were reproduced just in case they meant something.

Von Monakow stated that visual agnosia occurs only as an expression of diaschisis and tends to be transient. However, Lange quotes a number of cases in which this syndrome was stable over a period of years. One of the best examples is von Stauffenberg's case which persisted for 6 years. Lange takes the position that visual agnosia is not systematically related to impairment of general intelligence. Similarly, he concludes that there is no consistent relationship to peripheral optic conditions. Many of these patients have hemianopia but not all (20/30 von Stauffenberg's cases). Colour naming is frequently impaired, but in 6 of von Stauffenberg's cases it was spared. The dissociation of spatial orientation from object agnosia is also reviewed. Lange also says that agnosia can exist without alexia but he quotes himself and he mentions casually that reading is less disturbed in Lissauer's original cases than object recognition. The preservation of drawing and the issue of optic memory are all analysed, although not always with a decisive conclusion. Lange also mentions one of the most paradoxical phenomena in neuropsychology that one can see patients with agnosia who can quite successfully draw objects which they do not recognize. No attempts are made to formulate the mental processes that enable a patient to do this. The fact that Schn. could do these drawings was suggested as evidence for faking.

Balint's syndrome, simultanagnosia, and pure alexia are discussed in detail, especially the cases of Pötzl and Heidenhain which are described with an accompanying commentary. Cognitive psychologists will recognize the case of Beringer and Stein as that of deep alexia when she read 'elephant' instead of 'India'. There is an excellent discussion on colour agnosia, the concept of categorical perception of Gelb and Goldstein, and the contributions of Lewandowsky, Sittig and Heilbronner. Topographic orientations and constructional apraxia, acalculia, autotopagnosia, and tactile agnosia are all covered.

Lange provides his own observations and commentaries which are supported by references to other works. Altogether it is a poorly systematized, but rich resource of clinical insights: the fluctuation of performance in visual agnosia, the 'declining answer', when the patient recognizes something with a negative response ('That's not a cucumber', when pointing to the cucumber), false recognitions that involve optic confusions or the correct recognition of the objects presented previously, the compulsion to touch objects, and the convergence of multisensory impressions facilitating final recognition. Many of these case descriptions show that recognition is increasingly disturbed as the complexity of the stimulus increases. Impairment appears to be related to the conceptual summary of the details.

The section on apraxia is very much a review of Liepmann's work but Finkelnburg, Wernicke, Meynert, Morlaas and Hughlings Jackson are also credited. In fact, this chapter quotes from Liepmann in such detail that it is to some extent a duplication of Liepmann's review that appeared earlier. Nevertheless, the two are complementary and Lange's comments put Liepmann's paper in perspective. Finally, the section on localization is extensive and covers all aspects of cerebral localization of both the agnosias and praxis that were known at that time.

The third section of the book contains the translation of some of the works of Pötzl and his coworkers.

The first article by Hoff and Pötzl reports the anatomical findings, consisting of several cortical and subcortical lesions in the right hemisphere associated with the 'time acceleration phenomenon'. They discuss the process for motion perception in a time span. They correlate this with the suppression of motion perception in focal disease of other cases. Hoff and Pötzl deal with the issue of the body image, which was a frequently discussed concept at that time, in the next paper. A case report details the visual hallucinations of a man with cortical blindness in whom vertical gaze movements induced sensations of floating in his own body as in dreams of flying and falling. Another case report by Luers and Pötzl concerns inverted vision due presumably to a stroke in the territory of the posterior cerebral artery. The complex relationships of the vestibular system and the cerebellum are discussed in erudite detail. The authors assume a component that converts the environment for consciousness and this includes one process for the body image and another for the environment. This is similar to other visual phenomena described by Pötzl and coworkers, such as 'anisotrophia of visual space, disorders of depth perception, time-acceleration phenomenon, time-delay phenomenon, hemianopic hallucinations, etc.' Pötzl discusses the remarkable coincidence of smell and taste sensations and dream-like change of consciousness which has been termed 'uncinate' seizures, along with many of the other periepileptic phenomena. They are often transient and difficult to localize, although some of these patients had lobectomies and excision of tumours. There are widely ranging clinical, physiological and morphological parallels in the discussion that would be very unusual today.

Pötzl in his article on 'palinopsia' has an interesting discussion as to how the pathological study of the brain leads to the assignment of specialized function to certain parts of the brain. He challenges these concepts, but he concludes that a functional analysis of the brain lesions and their physiological significance must be made. Pötzl laments the fact that very few pathological cases can be found that have a clearly confined lesion in the occipital cortex and can be examined in detail. His patient perceived stimuli in multiples, following episodic loss of vision, visual agnosia and Balint's syndrome. The iterative reaction of palinopsia involved a constantly recurring positive image, a transient perseverative phenomena caused by a haemorrhage in the right posterior cerebral artery territory.

This collection of translations is not easy reading. It took me many weekends. Nevertheless, I think all behavioural neurologists and neuropsychologists interested in the phenomena of visual recognition and perception will find it not only useful but at times entertaining. Those with an interest in the history of medicine will also find the style and the depth of knowledge that is evident in these reviews most interesting. The translators increase the usefulness of these papers by having an author and topic index.

These papers may serve as a resource to researchers in the field and also a reminder to the research community in cognitive pyschology and neuropsychology that much of the newly described phenomena have, in fact, been discovered before.

Andrew Kertesz

Etiology of Dementia of Alzheimer's Type. Edited by A. S. Henderson and J. H. Henderson. Dahlem Workshop Reports (Life Sciences Research Report 43). 1988. Pp. 251. Bognor Regis: John Wiley. Price £32.95.

The Dahlem conferences were founded in 1974 by the German Association for the Promotion of Sciences and Humanities and the German Scientific Foundation to promote interdisciplinary exchange of information and ideas and international co-operation in research. Dahlem is a district in Berlin, whose Senate helps to finance the conferences. That such imaginative ventures can take place somewhere in Europe is a relief to those living in more 'penny-pinching' climates. What is remarkable, however, is that after a series of conferences in the fields of physics, chemistry and earth science, one has been devoted to dementia. Surely this must be an indication that this disorder is now recognized as of major importance to all western countries with their rapidly ageing populations. It also reflects the quality of the scientific work that is being carried out to elucidate the bases of this clinical syndrome.

This Workshop Report, edited by the Drs Henderson, is a stimulating one—very clearly written with 15 essays and 4 group reports. The former cover both clinical issues and the biological research that is currently bearing much fruit in the search for the causation of Alzheimer's disease. The latter are overviews of 4 areas concerning Alzheimer's disease, in which a subgroup of authors review current knowledge and point directions for further work. Particular emphases appear in this volume. One concerns the distinction between normal ageing and dementia, and another is the role of compensatory mechanisms that can postpone the outward manifestation of a pathological process in the brain. For both these issues, the interdisciplinary format of the conference has worked, for the reader can now consider them, both at the organismic and at the cellular level, in different chapters.

There is perhaps some repetition, and the ordering of the chapters does not seem entirely logical. These minor deficiences probably do not matter as this does not seem to be a book to read as a whole. One unusual feature is the presentation of the authors in group photographs during the book. These may well be of help at future conferences, enabling the 'stars' to be spotted!

ANTHONY MANN

Clinical Pediatric Neurology. A Signs and Symptoms Approach. By Gerald M. Fenichel. 1988. Pp. 401. Philadelphia: W. B. Saunders. Price £31.00.

Neither of the two main approaches to the subject of child neurology, system-based or symptom-based, is wholly satisfactory, and many writers have adapted a compromise or mixture of the two. This 'signs and symptoms' approach by Fenichel is probably the most successful of the second category, and an advance on the much earlier book by Lagos (1971) on *Differential Diagnosis in Pediatric Neurology*.

In his preface the author contrasts the problems involved in organizing such a textbook by chief complaint with the advantages for the reader confronted by a patient with a symptom and consulting the book for guidance. The problem posed by the occurrence of many symptoms as presenting features of a whole host of disorders is overcome by assigning the primary description of a disease to a single chapter (with some necessary exceptions) and by the generous use of tables to list differential diagnoses and to indicate the chapter with the most complete description of a disease.

The tables and figures used to display the differential diagnoses are excellent, and are valuable teaching aids. The Hurler phenotype, for example, is dissected in an algorithm based on distinctions of infant or later onset and biochemical findings which, when read in conjunction with two adjacent figures, encapsulates a great deal of information which is dealt with in more detail elsewhere in the chapter.

The clinical descriptions are a pleasure to read, bringing to mind a vivid picture of the clinical features and contrasting with the rather turgid accounts offered by many texts. Child neurology is still an area where the clinical approach, with a detailed history, is paramount, and the author's wide experience is reflected in his choice of words. His account of febrile seizures, on which much ink and breath are expended, is a model of brevity and clarity. Infantile spasms, the Lennox-Gastaut syndrome and many other manifestations of epilepsy are similarly treated in a practical and clear fashion, avoiding the almost theological minutiae which mar many descriptions.

Felicitous nuggets, worth quoting, occur in the section on Tourette's syndrome (which seems to be much commoner in the United States than the UK). 'A haircut is frequently the first unsuccessful intervention' (referring to the head-tossing movements), but desensitization may be the initial unsuccessful intervention when throat-clearing or cough-like noises are prominent and when an extensive evaluation for allergy has shown the child to be allergic. A commonsense approach to medication of tics and Tourette's syndrome is taken: the 'litmus test' for prescribing medication is determining whether the tics bother the child, and not whether they bother parents or teachers. It is good to be reminded that weakness of a child's neck muscles is often brought to attention while riding in a car when, with sudden acceleration or deceleration, the muscles cannot stabilize the head, which snaps backwards or forwards.

The author in his preface tells us that references were selected which are recent and easy to access, rather than original reports. The reader therefore should not complain, though he may regret, that original references to, for example, 'myoclonic encephalopathy' (Kinsbourne) and the dystonia-parkinsonism syndrome (Segawa), and the original evocative term 'dancing eyes syndrome', by which the former was first described, are not included. Some sacrifices clearly had to be made in the interest of brevity. The book is indeed a miracle of compression of a vast amount of information into 18 chapters in a relatively small volume.

The illustrative images (largely MRI), pathological and fundus photographs are excellent. I *think* I understand why there are only two clinical photographs (both of Duchenne dystrophy), and I wonder, with current trends, whether there is not scope for enlisting the help of the medical artist who may come to occupy as important a place in medical publications as he did in the prephotographic era. Better still, we might emulate Gowers and other masters of the past who embellished their works with their own drawings.

I would strongly recommend this book to all paediatricians, paediatric neurologists, and general neurologists, lucky enough to work in this fascinating field.

E. M. BRETT

Pediatric Neurosurgery. Second edition. *Surgery of the Developing Nervous System.* Edited by R. M. McLaurin, L. Schut, J. L. Venes and F. Epstein. 1989. Pp. 604. Philadelphia and London: W. B. Saunders. Price £93.75.

This volume (a second edition) has been prepared under the auspices of the Section of Pediatric Neurosurgery of the American Association of Neurological Surgeons. This accounts for all the contributors coming from North American clinics, of whom most will already be known as regular contributors to that hardy annual, *Concepts in Pediatric Neurosurgery* (published by S. Karger).

The standard of this book is very high. Its information content is good and its presentation excellent. The chapters cover all the expected subjects from developmental abnormalities through hydrocephalus, trauma, neoplasms and infections to vascular disease and finally to a miscellaneous section that contains chapters on functional neurosurgery, stereotactic procedures and paediatric neuroanaesthesia and intensive care.

The book is opened by a chapter on the normal development of the nervous system by Ronald Lemire and colleagues and then abnormal development is dealt with by Barry French. These chapters provide an excellent basis for the clinical sections that follow.

It would be invidious to pick out a particular chapter or author as a special recommendation—the 'team-effect' of the whole book is too important for that. There is also a distinct thread of practical experience running through many of the chapters which, combined with the up-to-date references, will make it a useful source of knowledge both for trainees and for those already established in the practice of paediatric neurosurgery.

RICHARD HAYWARD

Mechanisms of Epileptogenesis: The Transition to Seizure. Edited by M. A. Dichter. 1988. Pp. 287. New York: Plenum Press. Price $62.50.

Understanding the ionic events that underlie normal and abnormal electrical events in neurons and synapses has progressed enormously since Hodgkin and Huxley gave the first mathematical account of the conductances producing the squid axon potential in 1952. For each of the crucial ions (Na^+, K^+, Ca^{2+}) we now recognize several distinct voltage-gated channels, with different thresholds and rates of activation and inactivation, and dependence on the concentration of other ions. All of these may participate in epileptogenesis. Another vital basic issue is to define the factors providing the transition from normal activity to interictal and to ictal activity. Athough much is known about this transition, we cannot yet say what are the relative contributions made by the failure of inhibitory processes during sustained activation, by the enhancement of excitation that occurs with repetition or with the combination of non-NMDA and NMDA activation, or by the enhanced excitability produced by increases in extracellular [K^+] that result from discharges with paroxysmal depolarizing shifts.

This volume reports a meeting held in Philadelphia in September 1986. It is comprised of 16 contributions that discuss epileptogenesis from many angles, deriving information from cultured neurons, tissue slices, whole animal models of epilepsy and, in four chapters, from man. The presentation is overall very good, but there are lapses in proof reading, the contents list names only first authors of chapters and there are two separate ordering systems employed in the bibliographies (consecutive citation and alphabetical).

The contributions are readable and address the issues of the book in a coherent fashion. Thus the chapter on 'mechanisms of anticonvulsant action' focuses on ionic effects related to epileptogenesis. Two chapters are perhaps less central to the theme of the book but are highly rewarding, namely that by Gale and Browning on the anatomical substrates of rodent seizures, and the final chapter by Crandal and Sutherling on surgical treatment of the partial epilepsies.

Recent progress in basic neuroscience has fostered a resurgence of interest in the basic mechanisms of epilepsy. This volume reflects, and facilitates, this welcome development.

B. S. MELDRUM

Anticonvulsant Therapy: Pharmacological Basis and Practice. Third Edition. By M. J. Eadie and J. H. Tyrer. 1989. Pp. 367. Edinburgh: Churchill Livingstone. Price £45.00.

It was with great interest that I opened that third edition of *Anticonvulsant Therapy*. It is nine years since the second edition appeared, and at that time this was undoubtedly the best and most accessible source of the rapidly emerging data on the clinical pharmacology of the antiepileptic drugs. It was clear then that the appreciation of the pharmacological properties of the anticonvulsants as a group, more than the introduction of any individual agent, had been responsible for the greatest improvements in treatment. Since the second edition, no new major anticonvulsant drug has been introduced (at least until the introduction of vigabatrin in the UK this year), and the tempo of advances in pharmacology and therapeutics has slowed. The most recent developments have been in the techniques of measurements, and clinical applications (e.g. the measurement of free serum concentrations) have had little impact. This new addition, however, is timely, and it is well placed to sift and to take measure of the whole field. This it most successfully achieves and the book is to be highly recommended. It is divided into three sections. The first short section is a clear outline of the principles of treatment of epilepsy. It is specially good on the pharmacological aspects but perhaps less secure on the epidemiological or the more general features of epilepsy. The main (second) section of the book is divided into chapters each dealing with individual anticonvulsants (or related anticonvulsants). Each drug is covered in a systematic fashion with a short introductory piece and then subsequent sections on the chemistry, actions in man and in animals, mechanisms or action, biochemical effects, absorption and bioavailability, distribution, elimination, excretion, clinical pharmacokinetics, pharmacodynamic and pharmacokinetic interactions and side effects. This is a highly effective method, and the result is a comprehensive dossier on each individual drug. The whole text retains a pleasing unity and consistency, bearing the stamp of the personalities of the two authors—and this consistency is rarely seen in the more usual mutliauthored books. Both authors adopt a critical approach, avoiding the sometimes distorted claims for individual drugs, and citing the literature in an authoritative fashion. The third section, a new addition, is entitled 'The Use of Anticonvulsants in Practice', and is a detailed essay in therapeutics. Excellent in most parts, this is less good in some details. The chapter on status epilepticus for instance, is not up to the standard of the rest of the book. My main criticism of the text, however, is perhaps that it is too conservative, and the most recent or most contentious issues are not mentioned. Thus there is an inadequate treatment of the use of clobazam, of chlormethiazole in status epilepticus, of the treatment of serial seizures, or of vigabatrin or the other new anticonvulsants currently under evaluation. What competition does a book such as this have? There is a much larger multiauthored textbook devoted to antiepileptic drugs (with a new edition due this year), and also several more general volumes concerned with clinical aspects of epilepsy, and other books on recent advances in treatment. None has the advantages of this text, however, which is comprehensive and clear and which is a pleasure to read.

SIMON D. SHORVON

The CSF Proteins: A Biochemical Approach. By E. J. Thompson. 1988. Pp. 229. Amsterdam: Elsevier. No price.

After years of being responsible for CSF protein analyses performed at the Institute of Neurology, Queen Square, Dr E. J. Thompson now deals out some of his vast experience. His book reflects a critical rather than catalogue approach, and it is written in an unusual, very personal style.

After a useful glossary covering relevant nomenclature, the sources and principles for appearance of proteins in CSF are presented. Blood-CSF barriers are described in an unorthodox way. Most valuable is a section dealing with 'qualitative versus quantitative analysis' of protein in CSF, and also a chapter on some immunochemical methods and their limitations for the quantitation of individual proteins. A major part deals with the mathematics of multiple sources for the CSF proteins, and includes extensive evaluation of different formulae which have been proposed for clinical use during the last two decades for documentation of intrathecal synthesis of immunoglobulins. In his book, Dr Thompson promotes his own new logarithmic model of an existing formula. An appendix gives valuable notes on procedures for the detection of oligoclonal bands. 1000 references are included together with a cross index that can be used as a good start for the interested reader who wants to establish his own data base. Such a cross-indexed database is even available on floppy disc.

There are some criticisms. The recommendation to use primarily polyacrylamide gel electrophoresis for demonstration of oligoclonal bands will probably not be followed by most. The IgG level in CSF is not only determined by the serum level, barrier setting and local synthesis, but also by binding of IgG to Fc receptors and target structures as well as by half life which varies among different IgG subclasses. None of these factors can be taken into account in an undisputed manner, thereby reducing the value of all proposed formulae. I do not share the author's enthusiasm regarding his observations of a correlation between a major oligoclonal band called 'gamma 5 peak height relative to the internal standard of transferrin' and the severity of MS, or a correlation between level of free light chains and recent MS exacerbation, especially since we all know that there is little parallelism between appearance or disappearance of plaques detectable by magnetic resonance imaging, and clinical signs or symptoms. Few will be convinced enough to buy a densitometer for demonstration of oligoclonal bands.

Good reviews of CSF proteins in health and diseases are rare, and this book is therefore especially welcome. It should be enjoyable and valuable reading for everyone who is interested in CSF proteins in clinics, or includes CSF protein studies in research.

HANS LINK

Advances in Neuroimmunology. Edited by Cedric S. Raine. *Annals of the New York Academy of Sciences*, Volume 540. 1988. Pp. 745. Price $185.00.

This volume, published by the *Annals of the New York Academy of Sciences*, consists of the Proceedings of the Second International Congress of Neuroimmunology which was held in Philadelphia, USA, September 8–11, 1987. This reviewer was fortunate in being able to attend the congress which was universally regarded as extremely stimulating and successful. For this reason I found it particularly interesting to review these Proceedings and compare them with the 'live' events. The book certainly conveys much of the spirit of the congress and as the editor, Professor Cedric Raine, rightly points out in his preface, the enthusiasm, range of subjects covered, the high scientific standards and the interdisciplinary approach all underpin the clear emergence of neuroimmunology as a major specialty in its own right rather than an esoteric research area.

One-third of the book is devoted to proceedings of the didactic lectures given by the plenary session speakers, covering the fields of basic immunology and immune regulation, nervous system differentiation, clinical neuroimmunology and virus-induced disease and autoimmunity. Most of the lectures given on these topics were first-rate, as are the corresponding sections in the book. Some of these are particularly fine, for example the chapters on autoimmunity in demyelinating diseases (Waksman), HIV infections of the nervous system (Price and Brew), treatment of myasthenia gravis (Drachman *et al.*) and autoimmunity in neuromuscular disease (Newsom-Davis). The rest of the book contains the proceedings of the 16 workshops, each consisting of about 6–12 presentations. These cover a very wide range of topics, namely immunogenetics and gene regulation, T cell and immune system product localization in target tissue, lymphocyte lines and disease, antibodies and complement in autoimmunity, neural cell markers, glial-neuron interactions, cross-recognition between nervous and immune system antigens, MHC antigens on nervous tissue, monoclonal antibodies in AChR epitopes, immunotherapy of autoimmune diseases, monoclonal antibody and lymphokine therapy, clinical immunogenetics, AIDS and slow virus infections, molecular mimicry and virus-induced demyelination, neuroimmunomodulation and autoimmune models of demyelination. The actual presentations lasted about 5 minutes and this is reflected by the brevity of the articles, each one being about 2–3 pages long together with essential references. Much original data is presented and the general standard is high, although obviously the quality of the presentations and corresponding proceedings varies to some extent. The layout of both the congress and the book reflect what can be seen as one of the key factors in the success of both is that the longer articles based on the lectures give the specialist and nonspecialist reader a broad grasp of the basic principles of a variety of subjects, and these are then expanded by the wide range of research articles.

This book is undoubtedly as successful as the congress which it reports, and Professor Raine is to be congratulated on his organization of and participation in the congress as well as his successful editorship of this book. I found it a particularly stimulating volume and it will appeal to a wide variety of groups including clinical neurologists, neuropathologists, immunologists, virologists, anatomists, pharmacologists and many others. My only real concern was the fact that it is very expensive at 185.00 US dollars. Nevertheless it deserves to be on the shelves of all neurological and immunological libraries and it should certainly be read, and if possible bought by, any individuals with an interest in the growing field of neuroimmunology.

P. G. E. KENNEDY

The Human Central Nervous System. A Synopsis and Atlas. Edited by R. Nieuwenhuys, J. Voogd and C. van Huizen. Third edition. 1988. Pp. 437. Berlin: Springer. Price. DM 85.00.

This excellent book on human CNS structure is subtitled 'a synopsis and atlas'. The atlas makes up about one-third of it and is in 4 parts. The first of these deals with gross anatomy and the second, which is new, with the meninges and blood vessels. The third deals with sectional anatomy. The fourth consists of drawings of sections through the basal part of the prosencephalon, the brainstem and the spinal cord, correlating fibre tracts with nuclei. It also includes diagrams of fibre systems.

The fifth part of the book comprises approximately its final two-thirds. This is much more than a synopsis. It is very considerably expanded, particularly in its text, compared with the previous edition. Human CNS structure is described in 10 parts. Each deals with a particular functional system and gives a full account of its structure, its fibre connections and aspects of its function, correlated with comprehensive diagrams illustrating its connections. Clinical reference is, however, somewhat limited. The topics covered are: the cranial nerve nuclei; sensory systems, both general and special; ascending and descending reticular systems; the cerebellum; thalamic connections; motor systems; olfactory and limbic systems; association and commissural connections. Much new material is included, covering recent advances in knowledge. This is reflected in the very extensive bibliography numbering over 1500 references.

The greatly increased amount of material contained in the third edition compared with the second means that it is now too detailed for use as a basic text in present day crowded undergraduate medical curricula. Nevertheless, it will be very useful as an authoritative reference on detailed basic neuroanatomy for those concerned with all aspects and levels of neuroscience, particularly in regard to its superb illustrations. These are uniformly of very high quality indeed. All are very clear although some of those illustrating the cerebral vasculature are rather cluttered with detail.

JOHN P. FRAHER

The Prefontal Cortex. Anatomy, Physiology, and Neuropsychology of the Frontal Lobe. By Joaquin Fuster. Second edition. 1988. Pp. 269. New York: Raven Press. Price $86.50.

The prefrontal cortex is the cortex which receives a projection from the mediodorsal nucleus of the thalamus and which lies anterior to the motor and premotor cortical areas. There are few monographs devoted to the prefrontal cortex, and the second edition of Fuster's book is therefore very welcome. It has been expanded and provides a comprehensive review which includes many useful references to the recent literature. Fuster has separate chapters on the anatomy of the prefrontal cortex, neurotransmitters, the effects of lesions, and neurophysiology, each of which comprises an extensive survey. Much of the focus is on studies in nonhuman primates. In view of the development of the prefrontal cortex in primates, such studies are particularly relevant to understanding the functions and dysfunctions of this region of the cortex in man. These studies complement well Fuster's survey of investigations of prefrontal function and dysfunction in humans. The experimental studies in nonhuman primates implicate, for example, the dorsolateral prefrontal cortex in short-term memory tasks, particularly when a place is being remembered, and also the orbitofrontal cortex, which has gustatory and oflactory as well as visual inputs, in the flexible alteration of behaviour to rewarding and punishing stimuli and thus in emotional behaviour. Although the chapter on theories of prefrontal function is necessarily relatively undeveloped at this stage, the book as a whole provides a useful source of information on the prefrontal cortex which will be an important addition to any library which covers neuroscience.

EDMUND T. ROLLS

Neural Regeneration and Transplantation. Edited by Frederick J. Seil. *Frontiers of Clinical Science,* Volume 6. 1989. Pp. 294. New York: Alan Liss. Price $75.0.

This book is an attempt to present the growing field of nervous system repair to a wider audience of interested people not directly involved in this type of research. It succeeds in presenting a lively and exciting field in a style accessible to students and clinicians. The book is remarkable for its breadth of coverage—from muscle through peripheral nerve to spinal cord and brain. The most rapidly developing areas of research in intracerebral embryonic and peripheral nerve transplantation and growth factors are represented. There is an excellent contribution on the significance of glial scarring. Compared with the rather sombre picture of spinal cord injury, there is what many will see as an over-optimistic view of the current state of success in improving parkinsonian patients by adrenal autografts. This is balanced, however, by an important cautionary chapter on the immunological dangers of the possibility of autosensitization in intracerebral grafting.

Basically the modern resurgence of experimental and theoretical interest in nervous system repair stems from the feeling that research advances are carrying us to the point where useful interventions may become possible in patients. The success of this book will lie in its ability to get this feeling across simply and accessibly, and in remaining credible by not overwhelming the nonspecialist reader with opaque scientific detail leading to untestably optimistic claims. Judged by these criteria, the book is reasonably successful, and provides an up-to-date, readable and comprehensive coverage at a size that is handy physically and digestible mentally.

G. Raisman

From Neuropsychology to Mental Structure. By Tim Shallice. 1988. Pp. 462. Cambridge University Press. Price £15.00

The young discipline of cognitive neuropsychology has evolved from the recently growing convergence of cognitive psychology and neuroscience. The existence of the journal 'Cognitive Neuropsychology' establishes this and recently published scientific papers which are dedicated to the investigation of single cognitive functions and their impairment also try to provide a wide ranging dialogue between the two disciplines (e.g. LeDoux and Hirst, 1986; Ellis and Young, 1988). Tim Shallice's latest book provides the most comprehensive text that is currently available.

From Neuropsychology to Mental Structure is addressed both to cognitive psychologists and clinical neuropsychologists. Psychologists working in the cognitive field obtain a wealth of concentrated clinical observations and test results which are relevant for the development of neuropsychological theory. The discussion about clinically observed functional deficits in the context of more general psychological models could prove stimulating for neuropsychologists and possibly contribute to an understanding of patients' problems. Any reader, even those not particularly interested in cognitive psychology, would probably find the extensive discussion of methodological and programmatic considerations most profitable.

The author's intention is to depict the already achieved and possible future contributions of neuropsychological observations to the understanding of human information-processing mechanisms. For two reasons, according to Shallice, neuropsychological evidence is equivalent and often even superior to experimental psychological test results on normal subjects (which are traditionally evaluated as being superior). (1) Results obtained by experimental psychological tests are often ephemeral—they frequently disappear even if only one change relevant for the theory is made in the experimental situation or in the test material; also a change of the familiarity of the test person with the task has its influence. In contrast, the effects of brain lesions are often massive, persistent and also counterintuitive. In comparison to some filigree effects caused by experimental psychological testing, the neuropsychological observations therefore often relate to fundamental functional principles of the cognitive system. Neuropsychological observations frequently reflect basic functional principles of the cognitive system rather than the delicate effects obtained by experimental psychological methods. (2) Research in experimental psychology often promotes the further development of theories which are valid for certain defined experimental paradigms, whereas the impulse for neuropsychological research results directly from the fact that one has to understand the problems and deficits of brain-damaged patients. This is one reason why neuropsychological observations can be of greater theoretical and practical relevance for cognitive psychological questions than experimental psychological investigations on normal subjects.

The structure of the book is developed most stringently according to the author's intent to reveal the importance of neuropsychology for the understanding of human information processing. Based on a short history of neuropsychology, the first two chapters provide the essentials of cognitive neuropsychology. Chapters 3–8 illustrate, with several clinical examples, how the dialogue between neuropsychological and cognitive psychological research has led to a more profound understanding of human information processing (disturbances of short-term memory, reading, writing, language and object recognition). In the following 3 chapters, after having pointed out the positive aspects, the author deals with the limits, problems and possibilities of cognitive neuropsychology. Special interest is devoted to methodological (sources of artefacts in single and group studies) and epistemological problems (consequences of certain fundamental assumptions on the structure of the information-processing system and its influence on the attainment of knowledge). The final part (chapters 12 – 16) mainly covers open questions that in cognitive psychology are at present controversial (the structure of central processes and representation of knowledge, attention as a selective function, attention as a control of cognitive processes, the structure of memory and consciousness). Here Tim Shallice introduces neuropsychological observations which could be of importance for the further development of these theories.

From this short survey of the contents of *From Neuropsychology to Mental Structure* it is quite evident that in this case we are not confronted with a textbook on cognitive neuropsychology, in which the subject is dealt with in detail, but with a comprehensive description and discussion of a program. For a textbook covering the cognitive psychological aspects, topics such as elementary processes of perception, selective attention, problem solving and thinking processes, representation of knowledge and action control are either omitted or dealt with only partially. A highly differentiated index of key words, authors and patients quoted makes this book easy for readers to handle.

All case studies and the results of examinations which are presented as evidence are generally described in great detail, and the models discussed are illustrated and presented in structure-diagrams; basic statements of theoretical positions are often supported by quotations from the text. It is possible for the reader to understand a result or appreciate a model without having to consult the original literature. The detailed description, particularly with regard to the discussion of specific deficits, makes this book easy to read; however, there are certain parts, especially in the chapters dealing with methodology and epistemology, where the detailed information proves somewhat tiring. The rather lengthy explanations could also prove to be a handicap for persons seeking facts on a particular topic.

In sum, I consider this book to be the most explicit text on cognitive neuropsychology available at present, because of its extremely detailed and differentiated discussion of clinical cases and the broad spectrum of the cognitive psychological questions dealt with therein.

D. Y. VON CRAMON

ANNOUNCEMENTS

European Neurological Society

The second meeting of the European Neurological Society will be held at the Metropole Hotel, Brighton, UK, between June 30 and July 4, 1990. On June 30 and July 1 there will be six teaching courses on: Management problems in neurology I and II; Movement disorders; What you need to know about new techniques; Neuro-ophthalmology; and Neurorehabilitation. The scientific programme (July 2–4) includes five symposia (Retroviruses and the nervous system; Epilepsy; Basis for recovery in neurology; Behavioural neurology; Molecular basis of neuromuscular disease) and platform and poster sessions. Final submission data for abstracts: January 15, 1990. Further information from Concorde Services Ltd, 10 Wendell Road, London W12 9RT, UK, tel. 01 743 3106, FAX 01 743 1010.

Fourth Annual Magnetic Resonance Imaging Conference. Barrow Neurological Institute

This conference will be held at Marriott's Camelback Inn Resort, Scottsdale, Arizona, on March 3–7, 1990. Further information may be obtained from Kevin King, Radiologic Education Center, St Joseph's Hospital and Medical Center, 350 West Thomas Road, Phoenix, AZ 85013, USA.

International Symposium on New Horizons in Pediatric Neurosurgery/Neurology

This conference will be held in Tel Aviv, Israel on June 25–28, 1990. For further information, contact Professor Shaul Harel, c/o International Ltd., PO Box 29313, 65121 Tel Aviv, Israel.

Third International Workshop on the 'At Risk' Infant

The topic of this Workshop will be 'The Developmental Neurobiological Basis for Early Intervention, Animal and Human Models: Guidelines for Practice'. For further information, contact Professor Shaul Harel, c/o International Ltd., PO Box 29313, 65121 Tel Aviv, Israel.

Imaging the Central Nervous System (Including the Spine)

The Third Annual Course on this topic will be held at the Westin La Paloma Resort, Tucson, Arizona, on February 18–23, 1990, organized by the Medical College of Wisconsin and Continuing Medical Education. For further information, contact Continuing Medical Education Inc., 1101 W. North Avenue, Milwaukee, WI 53226, USA.

Second International Conference on Alzheimer's Disease and Related Disorders

This conference will be held at the Westin Harbour Castle, Toronto, on July 15–20, 1990. For further information, contact Dr Al Snider, Institute for Basic Research, 1050 Forest Hill Road, Staten Island, New York 10314, USA. Telephone (718) 494-5299, Fax (718) 698-3803.

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